THE JOURNAL OF PEDIATRICS

NOVEMBER 1960 *Volume 57 Number 5*

Waardenburg's syndrome

A syndrome of heterochromia of the irides, lateral displacement of the medial canthi and lacrimal puncta, congenital deafness, and other characteristic associated defects

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WAARDENBURG,[1] a Dutch ophthalmologist, first pointed out in 1950 that certain developmental anomalies of the eyelids, eyebrows, and nose root may occur in association with pigmentary defects of the irides and head hair and with congenital deafness as a genetically determined syndrome. Although the individual components of this new syndrome had been described previously, their associated occurrence in the same individual had escaped prior recognition.

The principal characteristics of the syndrome as described by Waardenburg are: (1) lateral displacement of the medial canthi of the eyes and of the inferior lacrimal puncta, (2) a broad, prominent root of the nose, (3) hyperplasia of the medial portions of the eyebrows, (4) white or gray forelock, (5) partial or total heterochromia of the irides, and (6) deaf-mutism.

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This paper was presented in part at the Sixty-Fourth Annual Session of the American Academy of Ophthalmology and Otolaryngology, Chicago, Ill., Oct. 11-16, 1959.

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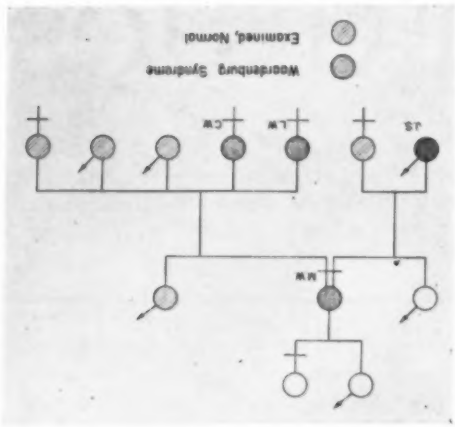

Fig. 1. Pedigree of family of L. W. and J. S. (Probands 1 and 2).

In 1951 Waardenburg[2] reported an extensive clinical and genetic study of the new syndrome and included a survey of the literature relative to the occurrence of the anomalies, separately and combined, in man and in other animals. From a study of sixteen family pedigrees, he concluded that the syndrome has an autosomal dominant inheritance with variable penetrance of the individual components. He estimated that individuals with this syndrome constituted approximately 1.43 per cent of all congenitally deaf persons in the Netherlands and that the incidence of the syndrome as a whole (with or without deafness) was approximately one person in 42,000 in the general population. This report appeared in a journal of genetics and, thus, may not have obtained adequate recognition by pediatricians, ophthalmologists, otologists, and others.

Since Waardenburg's initial delineation of the syndrome there have been but few additional reports and none in the American literature. Keizer[3] described another Dutch family in 1952 and Wildervanck[4] reported 5 additional Dutch cases in 1957. In 1958 McKenzie,[5] apparently unaware of Waardenburg's report, described a 4-year-old boy whose family pedigree showed 5 affected individuals in three generations. Partington,[6] in 1959, described an English family in which 5 members of four generations showed various components of the syndrome. In the same year, Fisch[7] reported the first histologic examination of the inner ear in this disorder. In this report he also summarized his observations of 35 affected individuals but illustrated only three family pedigrees, one of which (Pedigree No. 2) appears to be the same as that reported by McKenzie.[5]

It is the purpose of this paper to present our experience with this disorder in a group of subjects, to include the first reported instances in the Negro race, and to consider the potential contribution of the syndrome to the clarification of the pathogenesis of certain types of congenital deafness.

HISTORICAL BACKGROUND

In 1947 Waardenburg was consulted by an elderly, deaf-mute tailor with chronic

Fig. 2. M. W., mother of Probands 1 and 2. Right iris pale blue with limbal rim of brown pigment. Left iris normally pigmented. Definite white forelock. Normal hearing.

tearing and progressive impairment of vision. The features of the physical examination which most interested Waardenburg were the lateral displacement of the medial canthi of the eyes and of the inferior lacrimal puncta. Van der Hoeve,[8] in 1916, had first described these anomalies in 14-year-old, monozygotic twin girls who were deaf-mutes. Waardenburg's awareness of Van der Hoeve's original description caused him to wonder, "could it be pure chance that three deaf-mutes in our country should display this rare abnormality of the eyelids?" Upon presentation of the case to the Netherlands Ophthalmological Society in 1947, Goedbloed, an oculist at The Hague, showed Waardenburg another instance of the combination of deaf-mutism and lateral displacement of the medial canthi.[9] At about this time Waardenburg noted a photograph of a brother and sister who were described as having hypertelorism in Walsh's textbook, *Clinical Neuro-ophthalmology*.[10] The girl was totally deaf, the boy had impaired hearing, and both had white forelocks. The eye abnormality seemed to Waardenburg to be more characteristic of his syndrome than of hypertelorism in that the outer canthal distances appeared to be normal. In 1948, Waardenburg observed a 10-year-old girl, studied by Klein[11] in Geneva, who showed severe lateral displacement of the medial canthi, deaf-mutism, a white forelock, marked vitiligo, and other skeletal anomalies. It was the association of deaf-mutism and lateral displacement of the medial canthi in these four Dutch, two American, and one Swiss case that led Waardenburg to undertake a study of the inmates at five Dutch institutions for the deaf. He examined a total of 1,050 patients and found 13 with the eyelid anomaly. These individuals became the probands of the family investigations. It is interesting that it was not the more striking features of the disorder such as heterochromia or white forelock but the more subtle (and fortunately most common) defect of lateral displacement of the canthi that led to the delineation of the syndrome.

Fig. 3. J. S. Irides pale blue. Definite white forelock. Bilateral, profound loss of hearing.

Fig. 4. L. W. Medial portions of the eyebrows are white. Irides bilaterally blue. Bilateral, profound loss of hearing.

Fig. 5. C. W. Bilateral, pale blue irides. Unilateral, profound loss of hearing.

Fig. 6. L. W. Pale blue iris with brown pigment deposit at the limbus. In Negro children this pigment deposition is normally obscured by the dark iris.

Our interest in this disorder was aroused in 1956 when we examined a 6-year-old, Negro girl in the Out-Patient Department of St. Christopher's Hospital for Children prior to her admission to the Pennsylvania School for the Deaf. This child presented an arresting appearance because of an unusual light blue color of the irides. The medial portions of the eybrows were gray. Her mother had a light blue iris on the left and a white forelock (Fig. 2). It was learned that a half brother of the patient was a student at the Pennsylvania School for the Deaf and also had blue eyes (Fig. 3). We were unaware at this time of Waardenburg's report, but when these findings were described to Dr. Victor C. Vaughan, III, he cited Waardenburg's studies. Two months later a 4-year-old, Negro boy was seen in the Out-Patient Department for evaluation of a suspected defect of hearing. This child also had one blue iris and had serious impairment of hearing.

Following our initial observations, we described the syndrome to Mr. John Nace, Director of the Pennsylvania School for the Deaf. He and his teaching staff subsequently assembled a group of approximately 20 students who were either typical of or suspicious for the disorder. Upon detailed examination of these individuals, we found 6 instances of the syndrome.[12, 13] Unlike Waardenburg, we did not personally examine all of the students at this school; thus some cases may have escaped detection.

CLINICAL OBSERVATIONS AND PEDIGREES OF PROBANDS AND AFFECTED FAMILY MEMBERS

Proband No. 1. L. W., a 6-year-old Negro female, was examined in the Out-Patient Department of St. Christopher's Hospital for Children on June 19, 1956, prior to admission to the Pennsylvania School for the Deaf (Fig. 4). This child was known to be deaf and to have had excessive tearing, more marked on the right, since birth.

Physical examination revealed a hyperplastic, broad nasal root and medial hyper-

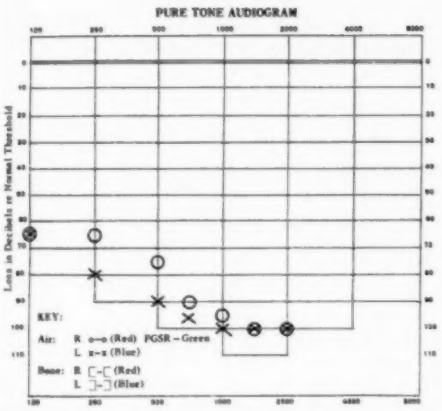

Fig. 7. Audiogram of L. W. showing profound, perceptive loss of hearing bilaterally.

plasia of the eyebrows with some white hairs present in the area. There was no white forelock. Scattered depigmented areas of the skin on both arms were noted. Both irides were pale blue and a heavy, brown pigment deposit was present about the limbi (Fig. 6). The inner canthal distance was 40 mm., interpupillary distance 54 mm., and the outer canthal distance 85 mm. The lacrimal puncta were small and displaced laterally 5 mm. from the medial canthi. There was fine pigment mottling at the periphery of the fundus. Slit lamp examination revealed the stroma of the irides to be thin and filamentous.

Audiometric testing disclosed a profound, perceptive loss of hearing bilaterally (Fig. 7).

Proband No. 2. J. S., a 14-year-old Negro male student at the Pennsylvania School for the Deaf, has known congenital deafness (Fig. 3). He is the half-brother of L. W., both probands having the same mother but different fathers (Fig. 1).

Physical examination revealed a striking gray forelock in the midline, a hyperplastic, broad nasal root, and medial hyperplasia of the eyebrows. The inner canthal distance was 48 mm., interpupillary distance 68 mm., and the outer canthal distance 98 mm. The inferior lacrimal puncta were 3 mm. from the medial canthi and 1 mm. inside the limbi. The irides were isochromic and of a striking pale blue color. Under slit lamp examination the iris frill was 2½ to 3 mm. from the pupillary margin and the stromal surface appeared atrophic. The limbal areas were well pigmented. There was fine pigment mottling at the periphery of the fundi.

Audiometric examination revealed a profound, bilateral perceptive loss of hearing.

Family History. M. W., the mother of probands 1 and 2, has most of the signs of the syndrome. She had 2 children by her first husband, one of whom is affected (J. S., Proband No. 2) and 4 children from her second marriage, 2 of whom are affected (L. W., Proband No. 1, and C. W.). The mother is acquainted with three brothers and one sister of her first husband, and with three brothers and three sisters of her second husband. She also knows her own mother, father, three brothers, two sisters,

Fig. 8. H. M. Striking heterochromia. Small blue segment in left iris at eleven o'clock and completely blue iris on the right. Profound loss of hearing bilaterally.

Fig. 9. G. R. Few strands of white hair, broad nasal root, displacement of the lateral canthi, and inferior lacrimal puncta.

Fig. 10. G. W. Congenital deafness. Note widened inner canthal distance and appearance of mouth.

a maternal uncle, two maternal aunts, four paternal uncles, three paternal aunts, her maternal grandmother and grandfather. One sister about whom little was known died. These relatives have not been examined by us but by history none were deaf, had gray forelocks, blue irides, or other ocular abnormalities.

Affected family members. M. W. has heterochromia. The iris of the right eye is pale blue with a limbal rim of brown pigment (Fig. 2). Ophthalmoscopic examination disclosed a normal, negroid fundus on the left and pigment mottling on the right. The inner canthal distance was 45 mm., the interpupillary distance 70 mm., and the outer canthal distance 100 mm. The inferior lacrimal puncta were displaced 6 mm. from the medial canthi. The medial portions of the eyebrows were hypertrophic and gray and there was a definite white forelock. Audiometric examination revealed normal hearing.

C. W., a 7-year-old daughter, was living with relatives in North Carolina at the time of our initial studies (Fig. 5). Some impairment of auditory acuity had been suspected by the mother. Through the cooperation of the school health authorities, audiometric testing was performed, revealing a profound, unilateral loss of hearing on the left. The child recently returned to live with the mother and has since been examined by us. Both irides were light blue in color. There was lateral displacement of the medial canthi and lacrimal puncta. The inner canthal distance was 45 mm.; interpupillary distance 52 mm. and outer canthal distance 80 mm. The inferior lacrimal puncta were 6 mm. from the medial canthal borders and situated inside the limbi. The left fundus was completely normal. There was no white forelock. Audiometric testing revealed a profound loss of hearing of the perceptive type on the right, and normal hearing on the left.

Comment. The transmission of the syndrome in this family is obviously through the mother. In addition to showing all of the manifestations of the disorder, with the

exception of deafness, she has had affected offspring from each of two marriages with unaffected husbands. Although none of the relatives could be examined, the absence of any other known affected family members suggests that the occurrence of the syndrome in the mother represents a new mutation. A significant observation in this family is the presence of isochromic, light blue irides in 3 affected individuals. This finding constitutes the strongest evidence recorded that lack of heterochromia does not eliminate the possibility that the irides are affected when they are both blue. Of additional interest is the presence of pigment mottling of the fundi of all of the eyes with blue irides with the exception of the right fundus of C. W. This observation lends support to the hypothesis that involvement of the fundal pigment may occur as part of the syndrome. The demonstration of unilateral, profound loss of hearing in association with other features of the syndrome indicates that this type of unilateral loss results from the genetic disorder occurring in the syndrome.

Proband No. 3. H. M., a 2-year-old Negro male, was brought to the Out-Patient Department on Aug. 27, 1956, because the grandmother felt that the child could not hear normally (Fig. 8). According to the mother, the color of the right iris changed from brown to blue at 2 weeks of age.

Physical examination revealed a well-developed child who did not respond to spoken words or noises. There was a broad, high nasal root and medial hyperplasia of the eyebrows but no white forelock. The inner canthal distance was 32 mm., interpupillary distance 53 mm., and the outer canthal distance 83 mm. The inferior lacrimal puncta were displaced 5 mm. laterally. The left iris was brown with a small area of blue in the upper medial quadrant. The right iris was light blue in color and flattening of the stroma was revealed by slit lamp examination. There was diffuse pigment mottling of the retinas bilaterally.

Audiometric testing by psychogalvanic skin response revealed a loss of 75 to 80 decibels in both the right and left ears, at 250 cycles per second; 80 db. at 500 cycles per second; and loss greater than 100 db. at all other frequencies. More recent testing by pure tone audiometry has confirmed the findings of bilateral, profound loss of hearing.

Family history. The proband has no siblings and neither parent has any of the characteristics of the syndrome.

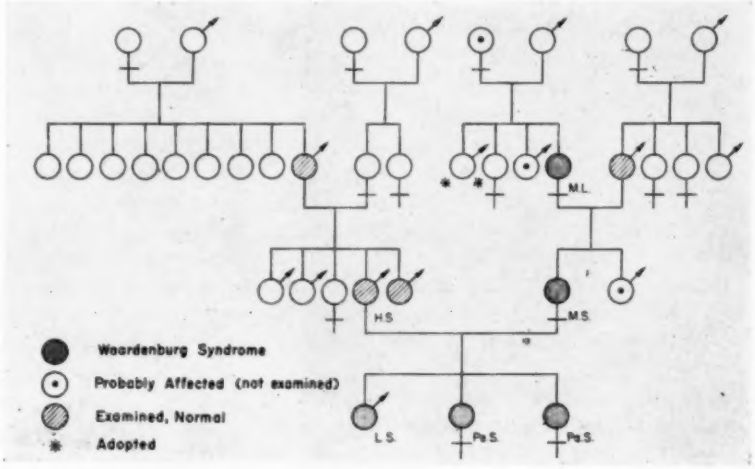

Fig. 11. Family pedigree of L. S. (Proband 7).

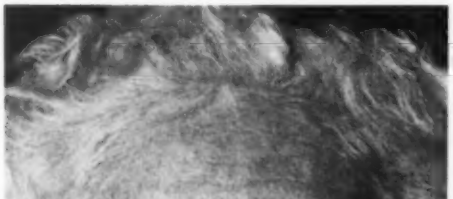

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Fig. 12. M. L. Maternal grandmother of Proband 7. Hair allegedly became suddenly and completely white at 40 years of age. Right iris completely blue, left iris is blue in lower half and brown in upper half.

Fig. 13. M. S. Mother of Proband 7. Bilateral pale blue irides. Note plucked eyebrows and dystopia of medial canthi.

The mother has 3 normal sisters; one brother died in infancy of unknown cause. None of these siblings are said to have had any of the manifestations of this syndrome, nor is there any suggestion of its presence in the maternal grandmother, grandfather, or any other maternal relatives.

The father is an only child and there is no known history of deafness, blue irides, or white forelock among his relatives.

It seems highly probable that the proband represents a sporadic mutation.

Proband No. 4. G. R. is a congenitally deaf, 15-year-old, white female student at the Pennsylvania School for the Deaf (Fig. 9).

Physical examination revealed a well-developed child with a few strands of white hair in the forelock, a broad nasal root, medial hypertrophy of the eyebrows, and vitiliginous changes of the abdominal skin and of the right lower leg. The inner canthal distance was 44 mm., interpupillary distance 60 mm., and outer canthal distance 87 mm. The inferior lacrimal puncta were 4 mm. from the medial canthi and 2 mm. inside the limbi. Both irides were very light blue. Slit lamp examination revealed retraction of the iris collarette, hypoplasia of the anterior border layer and stroma, and flattening of the iris pattern. There was fine pigment mottling at the periphery of the fundi which presented a tessellated appearance. Audiometric testing revealed bilateral, profound, perceptive loss of hearing.

Family history. The proband is an only child and there is no known deafness in the kinship. None of the family members have been examined to date, however.

Proband No. 5. B. M., a 4-year-old white

female student at the Pennsylvania School for the Deaf, was known to be congenitally deaf.

Physical examination revealed a child of normal size for her age. There was no definite white forelock with the exception of a few light hairs in the midline. There was a broad nasal root and mild, medial hypertrophy of the eyebrows which met in the midline. The inner canthal distance was 38 mm., interpupillary distance 54 mm., and outer canthal distance 80 mm. The inferior lacrimal puncta were 4 mm. from the medial canthi and the right nasolacrimal duct was obstructed. The irides were isochromic, of brown color, and appeared normal under slit lamp examination. There was fine pigment mottling at the periphery of the fundi. Reliable audiometric testing could not be obtained because of the apprehension of the child but it appears clinically obvious that she has a bilateral profound loss of hearing.

Family history. Detailed study of other members of this family has not yet been undertaken but some information is available by history. The patient's mother is con genitally deaf and has "very blue eyes." She had brown hair which changed to pure white early in life. The mother has 4 siblings none of whom are deaf, nor is there any other known deafness among her relatives. The father is also deaf. One of his 3 siblings is deaf and is the father of a deaf child who was examined by us and does not have the syndrome. The father's sister has 2 children, one of whom is partially deaf. This child was seen in our Out-Patient Department for hearing evaluation at a time when we were unaware of any relationship of this child to the M. Family. It was inadvertently noted that the father of the child had a white forelock but no other obvious characteristic of the syndrome. The paternal grandparents of the proband are both deaf.

Proband No. 6. G. W. is a 7-year-old white male student at the Pennsylvania School for the Deaf who has been known to be deaf since birth (Fig. 10).

Physical examination revealed a normally developed boy with a gray forelock, a broad nasal root, and medial hypertrophy of the eyebrows. The inner canthal distance was 40 mm., interpupillary distance 54 mm., and outer canthal distance 85 mm. The inferior lacrimal puncta were 4 mm. from the medial canthi and 1 mm. inside the corneal margins. The irides were isochromic and very pale blue. Under slit lamp examination the anterior border layer of the irides appeared thin and the stroma was filamentous and definitely hypoplastic. The fundi revealed very fine pigment mottling at the periphery. Audiometric examination revealed a profound, bilateral, perceptive loss of hearing.

Family history. This child was born out of wedlock. Nothing is known of the father or his family. There is no known deafness or other evidence of the syndrome in the mother or in any known member of her family. She has refused to participate in any further studies.

Fig. 14. L. S. Proband 7. Prominent gray forelock. Irides isochromic and pale blue. Similarity of facial appearance including nose and mouth of all patients is remarkable.

Fig. 15. Pe. S. Bilateral, pale blue irides and unilateral loss of hearing. Widened inner canthal distance gives appearance of strabismus.

Fig. 16. Pa. S. Isochromic, pale blue irides. Inner canthal distance 40 mm. at 1 year of age.

Proband No. 7. L. S. is a 10-year-old, congenitally deaf, white male student at the Pennsylvania School for the Deaf.

Physical examination revealed a well-developed boy for his chronological age. There was a prominent gray forelock, a high, broad nasal root, and medial hyperplasia of the eyebrows (Fig. 14). The inner canthal distance was 40 mm., the interpupillary distance 58 mm., and the outer canthal distance was 90 mm. The inferior puncta were placed 4 mm. from the inner canthi and 1 mm. inside the limbi. The irides were isochromic and pale blue with bilateral loss of stroma and flattening of the iris pattern revealed by slit lamp examination. There was a fine pigment mottling in the periphery of the fundus. Many brown nevi were noted on the torso but there were no depigmented areas.

Audiometric examination revealed a profound, perceptive type loss of hearing.

Family history. The pedigree of this proband's family is shown in Fig. 11. There was no evidence that the syndrome was present in any member of the paternal side of the family.

The syndrome was present with varying degrees of expression in 2 female siblings, the mother and maternal grandmother of the proband. Although no other relatives were known to be deaf, the maternal grandmother commented that "most of her relatives had very strikingly blue eyes."

Affected family members. Pe. S., a 5-year-old female, had medial hyperplasia of the eyebrows and a broad nasal root but no white forelock (Fig. 15). The inner canthal distance was 40 mm., the interpupillary distance 56 mm., and the outer canthal distance 80 mm. The inferior lacrimal puncta were situated inside the limbal borders. The irides were light blue and isochromic. The fundi revealed marked pigment mottling bilaterally. There were vitiliginous areas of the skin of the right wrist.

The parents had suspected that this child's hearing was not normal and audiometric testing revealed a unilateral, profound, perceptive loss of hearing (Fig. 17).

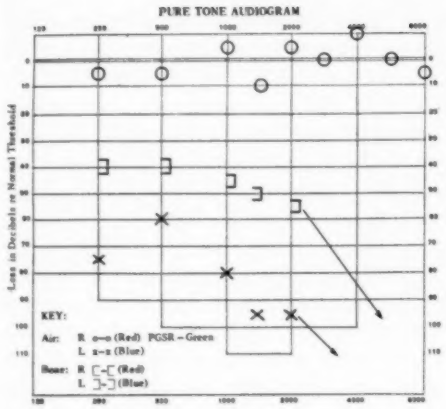

Fig. 17. Audiogram of Pe. S. showing unilateral, profound loss of hearing.

Pa. S., white female 1 year of age, had medial hyperplasia of the eyebrows, a broad nasal root, but no white forelock (Fig. 16). The inner canthal distance was 40 mm. and the inferior lacrimal puncta were situated within the limbal margins. The irides were isochromic and of the same blue color noted in the proband. Slit lamp and fundoscopic examination and audiometric testing were not performed. There was no clinical evidence of impaired hearing.

M. S., mother of the proband, had a white forelock, a broad nasal root, and medial hypertrophy of the eyebrows (this is not noticeable in the photograph as the eyebrows were plucked for cosmetic purposes) (Fig. 13). The irides were isochromic and of the same blue color as in the proband. The fundi revealed pigmentary mottling. Slit lamp examination was not performed. The inner canthal distance was 44 mm., interpupillary distance 64 mm., and outer canthal distance 90 mm. The inferior puncta were laterally displaced and situated inside the limbal margins. Areas of vitiligo of the skin of the dorsal surfaces of both wrists was noted but complete examination of the skin was not performed. Audiometric testing revealed an essentially normal pattern.

M. L., the maternal grandmother, had black hair and a white forelock in her younger years (Fig. 12). At the age of 40, her hair was said to have turned completely white within a period of one week. She had a broad, high nasal root and medial hyperplasia of the eyebrows which were completely white and met in the midline. There was partial heterochromia with a completely blue right iris. The left iris was blue in its inferior half and brown in the upper half. The inner canthal distance was 44 mm., the interpupillary distance was 63 mm., and the outer canthal distance was 90 mm. The inferior puncta were situated within the limbal margins. Fundoscopic examination revealed bilateral pigment mottling. There were areas of vitiligo of the dorsal surfaces of the wrists but complete examination of the skin was not performed.

Fig. 18. J. P. Increased inner canthal distance and dystopia of lacrimal puncta. No other stigmas of syndrome. Note tearing on right resulting from lacrimal duct obstruction.

She had been known to have unilateral loss of hearing which had been attributed to a fall in childhood. Audiometric testing revealed a unilateral, profound loss of hearing of the perceptive type.

There is no known consanguinity in this family and, thus, the occurrence of the syndrome in three successive generations is consistent with Waardenburg's hypothesis of an autosomal dominant form of transmission.

The presence of unilateral, perceptive loss of hearing in 2 family members exhibiting other manifestations of this syndrome adds further support to the theory that unilateral loss of hearing may be the result of the genetic disorder associated with this syndrome.

The presence of similar vitiliginous changes of the skin in members of three successive generations is also of interest and supports the hypothesis that such changes may be a part of the syndrome.

Proband No. 8. W. G. is an 18-year-old, congenitally deaf, white male. He was first seen at the time of our initial visit to the Pennsylvania School for the Deaf at which time only a superficial physical examination was performed. The parents have not permitted further examination. He has isochromic, light blue irides and a definite gray forelock. The eyebrows were normal and the lacrimal puncta were not displaced. The inner canthal distance was widened but the ocular measurements are not felt to be accurate. The inner canthal distance was less than 40 mm., the interpupillary distance, 69 mm., and the outer canthal distance, greater than 80 mm. Ophthalmoscopic examination of the fundi and irides was not done.

Family history. The proband is an only child. The parents have normal hearing and there is no known history of deafness in any relatives. The parents were unwilling to be interviewed, and, thus, the presence of any other stigmas of the syndrome among family members could not be ascertained.

Proband No. 9. J. P., a 4-year-old, Negro female, was seen in the Out-Patient Department of St. Christopher's Hospital for Children for evaluation of a chronic dacrocystitis and persistent rhinorrhea (Fig. 18). She was noted to have a broad nasal root and a widened inner canthal distance. The inner canthal distance was 35 mm., the interpupillary distance was 50 mm., and the outer canthal distance, 80 mm. The inferior lacrimal puncta were displaced laterally and there was a right dacrocystitis. The irides were bilaterally brown and the fundi were normal. There was no white forelock. Audiometric testing revealed a mild conductive loss in the high frequencies but bone conduction was normal. The chronic rhinorrhea was considered to be due to an allergic rhinitis.

The mother of the proband had gray streaking of the hair when she was approximately 20 years of age. At the time of

Fig. 19. S. H. Bilateral, pale blue irides. Normal inner canthal distance. Areas of depigmentation on skin of neck. Bilateral deafness.

examination she had superficial gray hairs laterally with a central, dark black forelock. The inner canthal distance was 38 mm. and the interpupillary distance was 74 mm. The puncta were in normal position. The irides were brown and isochromic and the fundi were normal. Audiometric testing was not done.

Family history. The patient is one of 3 siblings. A 14-month-old sister is said to have a slightly broadened nasal root and to resemble the proband in appearance. A maternal great uncle of the proband is said to have had a white patch of hair but there are no other known affected members of the maternal or paternal families.

Proband No. 10. S. H., an 8½-year-old Negro girl, was admitted to another hospital following an automobile injury. Because she was noted to be deaf and to have blue irides, she was referred to St. Christopher's Hospital for Children where she was seen on one occasion. The patient came to the clinic with a 15-year-old sister and the history is fragmentary.

The child was first suspected of being deaf at 1 year of age because she was not vocalizing. Blue irides had been present since infancy as far as can be recollected. She had been otherwise in normal health and had been attending a school for the deaf for 2½ years.

Physical examination revealed a girl who was normal with the following exceptions: The irides were pale blue with brown pigmentation at the limbus. The medial canthi were normal. The inferior lacrimal puncta were displaced approximately 4 mm. laterally. The medial portions of the eyebrows were only minimally hyperplastic. The interocular distances were as follows: inner canthal, 26 mm., interpupillary, 53 mm., outer canthal 85 mm. There was no evidence of grayness of the head hair or eyebrows. There were a few small areas of depigmentation especially on the neck (Fig. 19). Audiometric testing revealed bilateral, profound loss of hearing.

Family history. No other members of the patient's family are known to have blue irides, gray forelocks, or deafness, but the details of this family history are incomplete.

Proband No. 11. D. D., a 4-year-old Negro girl, was seen by one of us (R. D. H.) for ophthalmological evaluation and was then referred to St. Christopher's Hospital for Children. This child was born out of wedlock to a 16-year-old mother. Pregnancy and delivery had been uneventful but the infant had marked cutaneous depigmentation at birth.

The child is normal in all respects except for the following: (1) blue segment of the right iris from 12 to 1 o'clock and a blue segment of the left iris from 9 to 3 o'clock; (2) large areas of vitiligo on the right leg, the chest and abdomen, and the midline of the forehead (Fig. 20). All of these areas were said to have been much larger at birth but are gradually decreasing in size. Although repigmentation has occurred primarily in the periphery of these vitiliginous areas, islands of pigment deposition which grow and coalesce have also appeared. The area of vitiligo on the abdomen originally extended to the right iliac crest and that on the forehead extended to include the medial portions of both eyebrows. The head hair and eyebrows in the areas of affected skin are completely white. Although the skin has developed pigmentation in these areas, the hair has remained white. The ocular measurements are: inner canthal 28 mm., interpupillary 53 mm., and outer canthal 75 mm. Audiometric testing was not completely reliable but no impairment of hearing was detected.

Family history. The mother of this child is said to have had some graying of hair beginning in early childhood and at the age of 20 has moderately gray hair. She has grossly normal hearing, normal brown eyes, and no vitiligo. The mother's 18-year-old sister was examined and found to be normal and a 16-year-old brother and 15-year-old twin brothers are also said to be completely normal. Three younger siblings of the patient, also born out of wedlock, are normal.

The maternal grandfather is said to have developed gray hair in childhood and at the

Fig. 20*A*. D. D. Blue segments of irides. Marked vitiliginous changes of skin. No dystopia of canthi. No hearing defect.

Fig. 20*B*. D. D. Head and upper torso of patient shown in Fig. 20*A*.

age of 46 has completely gray hair. Slight impairment of hearing was first noted at 43 years of age. He has normal brown eyes and no vitiligo.

No other members of the family are known to have any of the components of Waardenburg's syndrome. None of the examined members of this family showed lateral displacement of the medial canthi.

CLINICAL DESCRIPTION OF THE SYNDROME

The individual components of the syndrome will be described in their order of decreasing frequency of expression as estimated by Waardenburg.[2]

1. Lateral displacement (dystopia) of the medial canthi and lacrimal points. In this anomaly there is an increased distance between the inner canthi of the eyelids, whereas the distances between the pupils and between the outer canthi are normal. This results in shortening of the palpebral fissures in the horizontal direction (blepharophimosis). This defect may, at first glance, give the impression of hypertelorism from which it is easily differentiated; in the latter condition the distances between the pupils and between the outer canthi as well as the distance between the medial canthi are increased. When one is familiar with this anomaly, it is as striking as the gray forelock or heterochromia of the irides. It was present in most of our patients and readily apparent even in the youngest (Fig. 16). Waardenburg[2] has given the range of normal measurements for the interocular distances of adults of mixed European populations. Since standards for children could not be found, a group was measured by us and the data are combined with those of Waardenburg (Table I). Waardenburg found that the inner canthal distance was 41 to 49 mm. in affected adults and that it had already reached 40 mm. in a 5-year-old boy. Our youngest patient had an inner canthal distance of 40 mm. at 1 year of age. An interesting fact that both Waardenburg[2] and Partington[6] have pointed out and with which we concur is that the anomaly is

Table I. Normal interocular distances (ranges expressed in millimeters)

	*Children**		*Adults†*	
	3-10 years	*10-16 years*	*Women*	*Men*
Inner canthal distance	22-30	28-34	24-37	26-39
Interpupillary distance	46-58	55-64	54-72	58-75
Outer canthal distance	70-80	81-90	74-92	77-96

*Data compiled by R. Harley (1 Negro and 19 white children).
†From Waardenburg.[2]

more easily recognizable in the patient than in photographs. Although the anomaly lends itself to simple objective measurements, it is unfortunate that in some reports[5, 7] none are recorded. In some patients little or none of the sclera on the medial side of the cornea is visible, giving the illusion of a convergent squint (Fig. 15).

The inferior lacrimal puncta are almost always displaced laterally and may be situated in front of the cornea. The superior lacrimal puncta appeared to be normal in all of our patients. Displacement of the inferior puncta may be associated with disturbances of lacrimal conduction, a complaint which was present in Waardenburg's first patient as well as in several of our children.

2. Broad prominent root of the nose. This characteristic is almost invariably associated with hyperplasia of the medial portion of the eyebrows. According to Waardenburg,[2] the median frontal process and portions of the two medial and lateral processes have grown hyperplastic during embryonic development at the cost of the neighboring ocular regions. However, roentgen studies of the nasal areas in 4 of our subjects have revealed no significant deviation from the normal. The peculiar nasal form is easily apparent even in young infants.

3. Hyperplasia of the medial portions of the eyebrows. Hypertrichosis of the eyebrows has been described as an inherited trait, often associated with a high nasal bridge. Usually, the eyebrows have been confluent and joined by hairs of normal color. In this syndrome, it is primarily the medial portions of the eyebrows that are hyperplastic. One would rarely expect to detect this trait in adult American women, since the practice of plucking these hairs is so common (Fig. 13).

4. Heterochromia irides (total or parital). Hereditary heterochromia iridum as an isolated finding is not common although instances have been reported as early as 1907. In a review of previously reported cases of simple heterochromia irides, Waardenburg[2] discovered at least 2 instances that were surely examples of this syndrome. Probably the first case of heterochromia on record is that of Anastasius, Byzantine emperor in the fifth century A.D. Anastasius was called "Dicorus," the Greek word for different colored eyes, and it was this distinguishing feature which allegedly contributed to his rise from an army private to emperor.[14] Unfortunately, Dicorus came of an obscure Dalmation family and nothing is known of his forebears.[15]

An interesting pictorial example of heterochromia is the painting of Leopold Zborowski by Amadeo Modigliani. Zborowski, a Polish poet who befriended Modigliani, had heterochromia which is faithfully reproduced in the painting. We have been unable to determine whether Zborowski had this syndrome; examination of photographs available to us shows hyperplasia of the eyebrows but a gray forelock or dystopia of the canthi is not discernible.

The degree of involvement of the irides is variable. One iris may be completely blue and the other completely pigmented (complete heterochromia) or both irides may be completely blue (isochromia). Not uncom-

monly the blue iris shows varying sized segments of pigmentation (partial heterochromia). Slit lamp examination of the affected irides reveals loss of stroma and flattening of the iris pattern. It is this hypoplasia which gives the characteristic pale blue color to the iris.

The patient who has isochromic blue eyes with the syndrome presents a special problem. Waardenburg[2] stated the problem as follows: "Do they lack heterochromia because having inherited other genetic factors causing them to have blue eyes the gene for the syndrome is unable to be expressed, or is the hypoplasia in such cases a complete and bilateral one?" In some of his subjects with isochromia, hypoplasia of the iris stroma was present and there was no doubt that the eyes were affected but in others the irides differed in no way from the normal. For purpose of genetic analysis, however, Waardenburg omitted all patients not having true heterochromia.

The observations made on our patients L. W., J. S., and C. W. are important since they present additional support for Waardenburg's belief that isochromic blue irides do constitute a part of the syndrome in some patients. Blue irides are extremely rare in the Negro and their association with the other features of the syndrome supports his belief beyond any reasonable doubt.[16] The affected irides of all members of this family were pale blue and hypoplastic.

5. White forelock. The forelock may consist of either a few strands or of a large shock of "blazing" white or gray hair in the midline. In the adult female this sign may escape detection owing to attempts to conceal it by tinting. Conversely, in accordance with the dictates of fashion, many women have self-induced white or gray forelocks.

Premature graying of the eyebrows, cilia, or both has been previously described in patients who almost certainly had this syndrome. L. W., a 7-year-old Negro child, demonstrated this finding (Fig. 4). This child had no gray forelock and it is possible that the gray eyebrows may represent its equivalent.

Other possible characteristics of the syndrome.

Abnormal depigmentation of skin. Although Waardenburg's examinations did not include a search for unusual depigmentation of the skin, this was noted on the forehead of one patient and elsewhere on the body of other patients. The case reported by Klein[11] showed very striking depigmentation of the skin. Mende[17] reported a four-generation pedigree with deaf-mutism and white forelock. This pedigree has been accepted by Waardenburg as an example of his syndrome because the photographs showed dystopia of the canthi. Affected members of this pedigree also showed areas of depigmentation on the arms, legs, hands, and feet as well as graying of the eyebrows.

Partington's[6] report described a depigmented area on the arm and forehead of a 2-year-old child whose mother also had a patch of "albino hairs" on the left leg. Fisch[7] also observed patients with areas of cutaneous depigmentation. Patient D. D. (Fig. 20) showed extensive depigmentation and bilateral, partial heterochromia. Since she did not have lateral displacement of the canthi or deafness one could argue that she does not represent a true example of this syndrome. However, the pigmentary defect involving the hair, skin, and irides in the patient and premature graying of the hair in the mother and maternal grandfather seems to justify their inclusion in this paper. We have observed several other patients with depigmentation of the skin but further study is needed to determine whether this abnormality is a component part of the syndrome.

Premature graying of the hair. Premature graying of the hair was noted by Waardenburg[2] in four kindreds, and he speculated that this may represent an equivalent of a white forelock in some individuals. This speculation is partially supported by the report of Partington[6] in which he described an individual who had a white forelock as a child and whose hair turned completely gray at 23 years of age. Our patient, M. L.

(Fig. 12), also is said to have had a white forelock in her youth and at 40 years of age her hair turned completely white within a short interval of time. Premature graying was a marked feature of the mother and maternal grandfather of patient D. D. (Fig. 20) although they themselves were otherwise normal.

Facial appearance. Waardenburg[2] described a characteristic facial appearance in this syndrome which he attributed largely to the abnormalities of the eyelid. Fisch[7] has described the jaw as "massive." The similarity of the physiognomy of our cases is contributed to by features other than the ocular abnormality and the prominent jaw. The face is rather square and, in addition to the broad nasal root, the nose itself is also typical. The nose appears thin owing to the decreased flare of the alae nasae and the tip tends to be rounded and slightly upturned so that the columella is usually easily visible in photographs. The lips are full with a pronounced "cupid's bow" and the distance between the corners of the mouth appears shortened. All of these findings result in a readily recognizable facies which should aid in the detection of the syndrome.

Roentgen examination of the skull of 5 of our patients revealed no abnormalities. The metopic suture was partially open in one patient, a finding present in 10 per cent of normal adults.[18] Fisch[7] stated that a metopic suture was present in "many cases" but neither the ages of the patients nor the number examined radiographically was given.

Pigmentary changes of the fundi. The fundi of some of our patients have revealed a peculiar pigment mottling especially marked in the periphery. Waardenburg[2] stated that "in a few cases the choroid and fundus seemed to take part in the pigment defect to a minor degree," but the changes noted were not described. He was unable to detect a significant difference in pigmentation of the two fundi of heterochromic individuals. In one of our subjects, the retinal pigmentary change was noted only in the eye with the blue iris but in other heterochromic individuals both retinas were affected. The frequency with which the pigmentary changes of the fundi have been noted suggests that it may constitute an integral part of the syndrome.

DEAFNESS AND DISTURBANCES OF PIGMENTARY METABOLISM

In animals. The occurrence of defective hearing in white animals has been known since 1769.[19] In 1829 Bree (cited by Wolff[19]) described a deaf white Persian cat which produced mixed litters but whose all-white offspring were invariably deaf. In the following year Blulenbach (cited by Wolff[19]) noted that Persian cats are often deaf. In 1847 Sichel[19] noted that white, deaf cats have blue irides. Many of the early workers described these white animals as albinos but it is known that the white of yellowed-eyed or blue-eyed cats is a dominant white[20] and that complete albinism is extremely rare in cats and dogs.[21] Although deafness occurs in white, as well as in the rare albino cats, it does not invariably occur in either.[20]

Wolff[19] reported the transmission of congenital deafness through three generations of white cats. More recently, Wilson and Kane[22] reported their observations on three generations of affected cats and described a white cat which had one green and one blue eye and which was deaf in both ears. This is contrary to the belief of earlier workers who reported that cats with one blue and one green eye are deaf only on the blue-eyed side.

Hereditary deafness associated with white color also occurs in bull terrier, Sealyham and Dalmatian dogs.[23] The authors have also learned of a horse, formerly owned by an ophthalmologist, which was all white except for a black patch on the head, which had one blue and one dark iris and was deaf. We have recently examined an all white, blue-eyed kitten which belonged to one of the pediatric residents. Free field audiometric testing of this cat proved it to be deaf. A few weeks after the examination

she was run over by a car as is wont to happen to deaf cats.

In man. In man, the association of pigmentary changes and deafness has been noted in other instances. Of particular interest is the Vogt-Koyanagi syndrome of uveitis, dysacousia, alopecia, poliosis, and vitiligo. This is an acquired, sporadically occurring disorder which has been attributed to various causes of which none have been firmly established.[24, 25] In the typical case, pronounced uveitis with eventual atrophy of the pigmented structures of the eye is followed at varying intervals by dysacousia. The deafness which is usually partial disappears over the course of months and is often associated with tinnitus. One to 3 months after the onset of the disease, alopecia appears, eventually followed by poliosis. The poliosis may involve not only the head hair but the eyebrows and cilia and occasionally the body hair. Vitiligo appears at about the same time and may involve any part of the body skin. Many theories of the etiology of this condition have been advanced. It has been frequently noted that the disease appears to follow a respiratory infection or severe emotional trauma. In an excellent review Hague,[25] in 1944, discussed the relationship of pigment disturbances of the eye, hair, and skin and dysacousia.

Deafness is also known to occur in patients with retinitis pigmentosa and is said to complicate 10 to 22 per cent of cases with the recessive form of the disorder.[26]

Histologic examination. Many investigators have performed histologic examinations of the inner ears of deaf cats and dogs. The literature on this subject has been completely reviewed by Innes and Saunders.[20] All authors have reported essentially the same pathologic changes, namely, total or partial agenesis of the organ of Corti, the spiral ganglion, and the cochlear nuclei. Wilson and Kane's[22] studies of deaf cats have demonstrated atrophy or complete disappearance of the cochlear duct. The only histologic observation on a human is that of Fisch[7] who examined the entire auditory pathway of a 3½-year-old girl who died of bronchopneumonia. Absence of the organ of Corti and atrophy of the spiral ganglion and nerve were demonstrated. Examination of the nuclei of the auditory pathway in the brain stem showed no abnormalities except for the cochlear root of the eighth nerve "which was thin, poorly myelinated and contained sparse nerve fibers."

GENETIC CONSIDERATIONS

The numbers of kindred studied by us are inadequate to permit significant genetic analyses but our findings support Waardenburg's hypothesis that the syndrome is inherited in an autosomal dominant manner. Of the kindreds studied by Waardenburg,[2] 83 siblings were found to be normal and 87 were affected, giving the expected 1:1 ratio for an autosomal dominant trait. There was no significant difference in the sex incidence of the eyelid abnormality, of the heterochromia, or of the white forelock. Deafness, however, was found in 21 males and in only 13 females, a difference consistent with the known fact that deaf-mutism from all causes is more common in males. Numerous instances of father-to-son transmission were found, thus excluding sex linkage. The sporadic cases are probably instances of new mutations. The first bearer of the mutation may present with any of the component parts of the syndrome or with any combination of them.

Penetrance. The degrees of penetrance of the individual anomalies comprising the syndrome as estimated by Waardenburg[2] are shown in Table II.

Table II. Frequency of individual anomalies*

		% *penetrance*
Total number affected relatives	161	
Dystopia		99
Broad nasal root		78
Hyperplasia of eyebrows		45
Heterochromia		25
Deafness		20
White forelock		17

*Adapted from Waardenburg's[2] data.

These estimations were considered by Waardenburg to be minimal values. Early in his study, the status of the eyebrows and nose root was not recorded, and as many of the individuals were known only from family history or from photographs, the estimation of the frequency of expression of the white forelock is also undoubtedly low. Balding in males, dyeing of the hair in females, or the presence of a few inconspicuous hairs could easily contribute to underestimation of the latter trait. If premature graying of the hair and/or the presence of gray eyebrows or cilia are considered equivalents of a gray forelock, the estimated penetrance for the anomaly would be increased. The estimated degree of penetrance of the iris involvement is also low since Waardenburg included only individuals showing true heterochromia. Our observations have established the fact that isochromic blue irides are, in some instances, part of the disorder.

The estimated 20 per cent penetrance for bilateral, profound loss of hearing is probably nearly accurate, but audiometric tests were not done on the affected families studied by Waardenburg.[2] Therefore, the gene effect in 80 per cent of the patients is unknown. Our demonstration of mild to moderate bilateral impairment of hearing and profound, unilateral loss of hearing in some individuals makes it clear that there may be considerable gene effect in patients who are not profoundly deaf.

The penetrance of the various components may vary considerably from kindred to kindred. Waardenburg[2] found that white forelock might be common in one kindred and rare in another; the same is true for deafness and for the heterochromia of the irides.

Frequency of the syndrome. At the time of our observations at the Pennsylvania School for the Deaf there were 471 students enrolled of whom 257 (54.6 per cent) were considered to be congenitally deaf. Six students or 2.33 per cent of the congenitally deaf were found to have this syndrome. This percentage is only a first approximation. First, since we did not examine all of the students in the institution it would tend to be low. Second, many of the students in the school were not classified as to etiology of deafness and the proportion of congenitally deaf is very probably low, resulting in a high percentage of children with this syndrome. In any event, this figure (2.33 per cent) may be compared with Waardenburg's finding of 1.43 per cent among the personally examined cases of congenital deafmutism in the Netherlands. If he had included 3 additional cases with heterochromia but without dystopia canthorum, the frequency would have been 1.78 per cent. Waardenburg[2] suggested that the same frequency would hold among noninstitutionalized deaf persons and estimated the occurrence of the syndrome (in association with deafness) to be one in 212,121 among the general population. The frequency of the syndrome with or without deafness would then be one in 42,000 individuals.

The number of congenitally deaf individuals in the United States is unknown; therefore, the syndrome in the general population cannot be accurately estimated. In 1958 there were 34,632 individuals with profound loss of hearing attending residential or day schools for the hearing handicapped in the United States.[27] Using either our figures or those of Waardenburg, we can estimate that approximately 400 of the individuals in the schools for the deaf have this syndrome. We have demonstrated that partial or unilateral loss of hearing may occur in this syndrome, a finding which must have been present in some of Waardenburg's subjects. Therefore, the estimated occurrence in the general population of this syndrome as a cause for some form of impaired hearing would be higher than the one per 212,121 as originally estimated by Waardenburg.

CONCLUDING REMARKS

The association of defects of pigmentation with anomalies of various body structures and with deafness has been a subject of

interest to many investigators and numerous theories of the pathogenesis of these related occurrences have been proposed. Most recently Fisch[7] has attempted to relate the abnormalities occurring in Waardenburg's syndrome to a genetic defect of the neural crest. Despite the many theoretical postulations proposed, the pathogenetic mechanisms of the anomalies present in this syndrome remain unknown and, as Waardenburg aptly states, "the time is not ripe to delve deeper into the question of the phenogenetic mechanisms or to attempt to solve various other genetic and embryological problems posed by the new syndrome."

The significance of this syndrome at the present lies in the recognition of its association with congenital nerve deafness. Although the relationship between the pigmentary defects and the deafness is purely speculative at this time, the documentation of this syndrome in the American literature may prove a stimulus to others for further investigation in these areas.

SUMMARY

1. Individuals with Waardenburg's syndrome, including the first reported instances in the Negro race, have been presented.

2. This syndrome consists of:

A. Lateral displacement of the medial canthi of the eyes and of the lacrimal puncta.

B. A hyperplastic, broad nasal root.

C. Hyperplasia of the medial portions of the eyebrows.

D. Partial or total heterochromia iridum or isochromic, hypoplastic blue irides.

E. Congenital deafness or varying degrees of partial deafness.

F. White (or gray) forelock.

3. The syndrome is genetically determined and transmitted in an autosomal dominant manner with varying degrees of penetrance of the individual characteristics.

4. Possible additional characteristics of the syndrome have been discussed. These include premature graying of the hair; abnormal depigmentation of the skin; pigmentary changes of the fundi and a characteristic facial appearance.

5. It has been roughly estimated that 2.0 per cent of congenital deafness in the United States may result from this disorder.

6. A summary of the pertinent literature relative to the occurrence of defects of pigmentation and deafness in man and in animals has been presented.

The authors are indebted to Mr. John Nace, Headmaster of the Pennsylvania School for the Deaf, Philadelphia, Pennsylvania, for his cooperation in making available the facilities of the school and for his personal services. We also wish to acknowledge the assistance of Dr. Milton Brutten and Mrs. Marguerite Eversden for the audiometric studies. We are indebted to Dr. Costas A. Zervos for referring Proband 10 to us.

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The prognosis of subdural effusions complicating pyogenic meningitis

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THE development of antibacterial agents effective in the treatment of acute pyogenic meningitis has been associated with the recognition of concomitant or late sequelae in surviving patients. Among the most common of these complications is the occurrence of collections of fluid in the subdural space. Penfield[1] described the diagnosis and management of a subdural effusion in a boy with chronic otitis media, and Spitz, Pollak, and Angrist,[2] in reporting autopsy findings in 2 cases, first described the association of meningitis and subdural empyema in which there was no evidence of suppurative disease in the ears or sinuses. However, it was the report of McKay and colleagues[3] that called attention to the syndrome in which collections of sterile fluid complicate the otherwise successful treatment of pyogenic meningitis. The original cases were all of meningitis due to *Hemophilus influenzae* type b, but it soon became evident that subdural effusions could occur in any type of bacterial meningitis.[4-12] Occasionally infected subdural effusion can be differentiated from the nonsuppurative variety by the presence of erythema, induration, and local heat in the area of the anterior fontanel.[5] However, it is not generally possible to make this differentiation,[13] and these conditions are usually considered together.[14]

Although subdural effusion is now well recognized, there is considerable divergence of opinion with regard to its incidence, significance, and optimal management. McKay, Ingraham, and Matson[4] reported 50 cases in which subdural fluid was found during treatment of purulent meningitis and estimated the incidence of effusions as occurring in about 50 per cent of their infants with meningitis. Similarly, Smith, Dormont, and Prather[8] reported upon 43 patients with meningitis under 2 years of age, 20 of whom were found to have subdural effusions. These investigators recommended that diagnostic subdural taps be performed regularly in patients recovering from purulent meningitis. Stevens and Williams[15] have also stated

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that subdural effusions were present in approximately half of their patients with purulent meningitis. On the other hand, a number of authors, in reports dealing primarily with meningitis[16-18] as well as 1 group reporting experience with effusions and other sequelae,[14] have reported a considerably lower incidence of effusions which ranged from 6 to 17 per cent, although in 1 of these series[17] the incidence of effusions with meningitis due to *Hemophilus influenzae* type b was 50 per cent. The implication of these data is that routine subdural taps may not be necessary in patients with purulent meningitis. Pediatric opinion has often represented this point of view, and Margaret Smith, [13, 19] who originally suggested the routine procedure, has more recently recommended against it. Alexander,[20] in a recent review, has continued to recommend the routine performance of subdural taps in all patients with meningitis and open sutures.

McKay, Ingraham, and Matson[4] found subdural membranes in the majority of their patients with postmeningitic effusions and recommended treatment as described by Ingraham and Matson[21] for chronic subdural hematoma: decompression by repeated aspirations followed by trephination in search of subdural neomembranes and removal of any present through a craniotomy. Williams and Stevens[15] have argued theoretically that craniotomy should be performed in every instance. The observation that, in a number of instances, repeated drainage by means of subdural taps was followed by a drying up of the effusion and apparent complete remission was first made by Smith, Dormont, and Prather.[8] This has been the predominant pediatric experience.[13, 14, 20]

Optimal management of these patients can best be determined by careful comparison of the long-term results of the various methods recommended. For the purpose of obtaining information relating to this question, follow-up examinations were initiated for patients treated for purulent meningitis beginning in 1949. Since it is not possible to be certain of the presence or absence of effusion in patients not subjected to subdural tap, only those patients in whom this procedure was carried out were followed. In this study, patients found by subdural taps not to have effusions serve as controls for those in whom effusions were found.

Table I. Description of the series

Result of subdural taps	*No. of children with meningitis*	*Died*		*Follow-up examination*
		No.	*%*	
Effusion present	67	10	15	49
No effusion present	42	6	14	22
Not tapped	219	28	13	0
Total	328	44	13	71

CLINICAL MATERIAL AND METHOD OF STUDY

During the 10-year period from January, 1949, to January, 1959, subdural taps were performed in 109 (34 per cent) of 320 patients admitted to The Harriet Lane Home with acute purulent meningitis (Table I). Effusions were found in 62 per cent of those in whom taps were carried out. Of these 67 patients, 10 died and 49 were examined at follow-up by the authors. Of the 42 patients in whom subdural taps were negative, there were 6 deaths and 28 were seen at follow-up examination. Thus, definitive follow-up data were available in 88 per cent of patients with effusions and 67 per cent of those with negative subdural taps, or 80 per cent of the total study group. The analysis of follow-up data (Tables VIII to XIII) was based on the 59 patients in whom taps were positive and the 28 in whom taps were negative in whom definitive follow-up data were available, while in the description of the details of initial hospitalization (Tables IV to VII) the 109 patients in whom taps were performed have been presented. The mortality rate of each group did not differ from that of the larger group in whom subdural taps were not performed.

Table II. Age incidence

Age	*Subdural effusion*			*No subdural effusion*		
	*Followed**	*Not followed*	*Total*	*Followed**	*Not followed*	*Total*
0 to 6 months	24	4	28	15	7	22
7 to 12 months	27	4	31	9	3	12
13 to 18 months	7	0	7	3	2	5
19 to 24 months	1	0	1	0	2	2
2 to 4 years	0	0	0	0	0	0
Over 4 years	0	0	0	1	0	1
Total	59	8	67	28	14	42

*Includes patients who died.

Table III. Duration of follow-up

Duration of follow-up	*Subdural effusion present*	*No subdural effusion*
0 to 6 months	1	0
7 to 12 months	4	4
1 to 2 years	5	1
2 to 4 years	14	3
4 to 6 years	7	5
6 to 8 years	10	4
8 to 10 years	8	5
Dead	10*	6†
Total	59	28

*Nine died during the acute stage of meningitis. One had 2 attacks of pneumococcal meningitis 6 months apart, and died suddenly 1 month after the second with normal findings in the cerebrospinal fluid and negative subdural taps.

†Four died during the acute stage of meningitis and 1 died 21 months later of hydrocephalus. The sixth died 6 months later; autopsy did not reveal the cause of death.

Table IV. Classification according to the organism recovered from the cerebrospinal fluid

	Subdural effusion	*No subdural effusion*
H. Influenzae	30(4)	17(5)
Pneumococcus	20(5)	5(0)
Meningococcus	6(0)	8(0)
Salmonella	2(0)	0
E. coli	0	2(0)
Others	0	2*(1)
Not recovered	9(1)	8(0)
Total	67(10)	42(6)

The figures in parenthesis signify the number of deaths in each category.

*In one patient, infection was due to *Staphylococcus aureus* and in the other to *Proteus vulgaris*.

The ages of the patients are shown in Table II. Fifty-nine (88 per cent) of those with effusions and 34 (81 per cent) of those without were under 12 months of age. Subdural taps were performed in only 4 children over 18 months of age.

The duration of follow-up is shown in Table III. Among the survivors, 80 per cent of those who had had effusions and 77 per cent of those without were followed for over 2 years. The corresponding values for more than 4 years of follow-up were 51 per cent and 64 per cent, respectively.

In each case the clinical record was reviewed. At follow-up examination, historical details were reviewed with the parent. Emphasis was placed on details of development, intellectual capacity, and behavior. Physical examination was carried out with particular attention to the neurological examination. A clinical estimation of developmental maturity and intelligence level was made in each case. Details of performance and testing of children who had reached school age were obtained from the schools. Psychometric testing has been carried out in most of the moderately and severely retarded patients; in others, testing has been carried out for clinical or scholastic reasons. Routine follow-up testing of these patients has confirmed the clinical impression in the small group of patients studied. Communicative behavior was assessed by inquiry into language and speech development, by evaluation of language comprehension and speech, and by measurement of auditory function.

Standard speech-hearing and discrimination tests were employed wherever possible, and in the other children gross response was observed in the soundproof room. Auditory and communicative behavior was observed in free play and structured situations. Pure tone audiometry was determined in children who were able to cooperate. Psychogalvanic skin resistance audiometry was performed in the others.

RESULTS

Part I. Aspects of the acute illness.

Bacteriology. The etiology was established by isolation of organisms from cultures of the cerebrospinal fluid (Table IV). The most common causative agent was *H. influenzae* type b: 45 per cent of those with subdural effusions, 40 per cent of those with negative taps, and 31 per cent of 219 patients not subjected to subdural tap. The incidence of pneumococcal meningitis was 30 per cent in the group with effusions and only 12 per cent in those without effusions. Among patients with pneumococcal meningitis in whom taps were performed, 80 per cent were positive. Meningococcal meningitis was less common among the patients with positive taps than among those with negative taps. The differences among the groups infected with these 3 organisms were significant ($\chi^2 = 7.2$, $P < .02$). Effusions were found in both patients with Salmonella meningitis, whereas taps were negative in 2 instances of infection with *Escherichia coli* and in 1 each with *Staphylococcus aureus* and *Proteus vulgaris*. Of the 17 patients in whom the etiological agent was not recovered, 9 had effusions. Positive blood cultures were obtained in approximately equal proportions of the groups with and without subdural effusions.

Clinical aspects of the acute meningitis.

SEX AND COLOR. There was a predominance of males among the patients with subdural effusions (Table V). Whereas 64 per cent of the patients with effusions were males, there was an approximately equal distribution of males and females in the patients who had negative taps. It was also noted that whereas slightly less than half of the patients without effusions were Negroes, 73 per cent of those with effusions were Negroes (Table V). The distribution of the different infecting organisms among the males and females was similar. However, the predominance of Negroes among the patients with effusions was much more marked in patients with pneumococcal meningitis than in those with disease resulting from *H. influenzae* or Meningococcus ($\chi^2 = 9.7$; $P < .02$).

Table V. Sex and color

	Male	*Female*	*Total*	*White*	*Negro*
Subdural effusion	43	24	67	18	49
No subdural effusion	22	20	42	23	19

Considerable variability was observed in the interval between the onset of symptoms and the commencement of adequate treatment in the patients with and without subdural effusions (Table VI).

CLINICAL MANIFESTATIONS. The clinical features at the onset of meningitis were similar in the patients who developed subdural effusions to those in whom subdural taps were negative (Table VI). However, the development of coma, convulsions or neurological abnormalities after the initiation of adequate antibacterial therapy was somewhat more common in the group with effusions.

Data were not available to permit evaluation of the suggestion by Williams and Stevens[22] of a relationship between the amounts of fluid removed in the course of diagnostic lumbar puncture and the development of subdural effusions.

Indications for subdural tap. The reasons for which subdural taps were performed are listed in Table VII. In some patients multiple indications were present. On the other hand, a number of subdural taps were performed in the absence of specific clinical indications, because, at various times during the period under study, this procedure was routine in patients with an open fontanel

recovering from purulent meningitis. Sixty-four per cent of the negative taps were carried out as routine procedures. However, 23 (34 per cent) of the subdural effusions were discovered by the performance of the routine procedure in patients without specific indications. Considered in another way, subdural taps were performed as a routine procedure in 50 patients, in 23 of whom subdural effusions were found. The utility of specific indications for subdural taps may be judged by the relative incidence of these findings in patients in whom effusions were present and absent, as well as by the relative promptness with which the manifestations disappeared following subdural tap. Considered in this way, a defervescence in a patient with purulent meningitis followed by an exacerbation of fever appeared to be a good indicator of the presence of subdural effusion. Convulsions were noted in 15 of the patients with effusions and stopped following subdural tap in 9 of them. Persistent irritability was more common in the patients with effusions than in those in whom effusions were not found by subdural tapping, and often disappeared promptly following decompression. Persistent fever, lethargy, or coma, and evidence of recurrent or persistent meningeal infection were more common in the group with positive subdural taps, but decompression was not regularly associated with the disappearance of these findings. Vomiting, neurological abnormalities, and signs of increased intracranial pressure were less reliable indicators of the presence of effusion. Transillumination was not carried out with sufficient frequency in the present series to permit assessment of its utility. Electroencephalography was performed in 12 patients with subdural effusions during the acute stage of meningitis. Asymmetry, in which the lower voltage was on the side of the lesion, was present in 5 patients. In 1 patient seizure discharges were observed and in 6 normal tracings were obtained. Records were also obtained in 6 patients in whom subdural taps were negative. Of these, 4 were normal, 1 had voltage asymmetry, and 1 showed seizure discharges.

Table VI. Relation between clinical features and the incidence of subdural effusion in 109 cases of acute purulent meningitis

Clinical data	*Subdural effusion*		*No subdural effusion*	
	No. of patients	*% of total in whom observed*	*No. of patients*	*% of total in whom observed*
Interval between commencement of symptoms and initiation of treatment				
Less than 24 hours	16	24	15	36
24 hours to 4 days	31	46	10	24
More than 4 days	20	30	17	41
Coma				
At onset	11	16	7	17
During treatment*	4	6	0	0
Convulsions				
At onset	22	33	11	26
During treatment*	9	13	2	5
Neurological findings				
At onset	11	16	7	17
During treatment *	10	15	2	5
Fever†	64	95	37	88
Signs of meningeal irritation†	45	67	25	60
Increased tension of the anterior fontanel†	39	58	19	45
Vomiting†	33	49	16	38
Acute otitis media†	15	22	7	17

*Excluding those in whom the finding was present at onset.

†On admission.

Table VII. Indications for subdural taps

Indication	Subdural effusion		No subdural effusion	
	No. of patients	*No. in whom the sign disappeared within 24 hours after tap*	*No. of patients*	*No. in whom the sign disappeared within 24 hours after tap*
Routine procedure	23	0	27	0
Recurrent fever after normal temperature 24 hours or more	7	5	1	1
Persistent fever after 48 hours' treatment	10	1	1	0
Persistent lethargy or coma after 48 hours' treatment	9	1	1	0
Persistent irritability after 48 hours' treatment	6	3	2	0
Persistent vomiting after 48 hours' treatment	4	2	3	1
Convulsions	15	9	3	1
Neurological signs	5	2	3	0
Signs of increased intracranial pressure	3	0	1	0
Recurrent or long persistent infection	4	1	1	0

In some patients, multiple indications were present. None of the other indications were present in the patients listed as having the routine procedure.

Effusions were detected at the first tap in 52 patients and at a subsequent tap in the other 15. The frequency of multiple subdural taps was greater in the group of patients without effusions among whom 17 underwent more than 1 attempt to find subdural fluid.

Nature of the subdural fluid. The gross appearance of the subdural fluid is shown in Table XII. In the majority xanthochromic fluid was obtained. The fluid was sterile in all but 6 patients, in 4 of whom follow-up is known. Purulent subdural fluid was associated with a positive culture in only 1 instance in which pneumococcal meningitis was grossly inadequately treated. The other patients with infected subdural fluid included another patient with inadequately treated pneumococcal meningitis and a patient with Salmonella meningitis in whom positive cerebrospinal fluid cultures were obtained over an extended time in spite of vigorous therapy. In 2 patients with *H. influenzae* meningitis and in 1 with meningococcal meningitis, positive subdural fluid cultures could not be correlated with unusual details of management or clinical course. The protein content of the subdural fluid was not investigated with sufficient regularity or precision in these patients to permit quantitative correlations, but the protein content of the fluid was generally considerably higher than that of the cerebrospinal fluid. Protein levels of over 300 mg. per 100 ml. were found in 71 per cent of 45 instances in which the determination was made.

The volume of fluid obtained at any individual subdural tap is often a function of the amount the operator is willing to collect before terminating the procedure. Consequently, there was considerable variation in the amounts of fluid recovered in this series. In 30 instances (45 per cent), the volume of fluid obtained was never more than 15 ml., which conforms to the generally recommended procedure, and in 57 per cent the volumes were always less than 30 ml. In 12 patients, over 60 ml. was removed from a single effusion site on one or more occasions. Effusions were bilateral in 32 patients.

Treatment. The incidence of subdural effusions in children who had received sporadic antibiotic treatment prior to admission to the hospital did not differ significantly from that in those not so treated. Details of the antibiotic treatment of the purulent meningitis were also quite similar in patients with and without effusions. Corticosteroid therapy was used in only 6

patients, 5 of whom had effusions. The fact that only 1 of these patients appeared normal at follow-up may simply reflect the use of steroids in very ill patients. It suggests, however, as do the data of Lepper and Spies,[23] that steroid treatment of purulent meningitis may increase the likelihood of complications.

LOCAL TREATMENT OF THE EFFUSION. The local treatment employed for subdural effusion is presented in Table XIII. In 45 infants treatment consisted of repeated drainage by subdural tap. Of these, 4 died before adequate treatment could be completed. Treatment was terminated in 8 infants before negative taps were obtained. Taps were performed on the remaining 33 patients until the subdural space appeared dry. This necessitated repeated subdural taps for less than 1 week in 12 instances, for 1 to 2 weeks in 5, and over 2 weeks in 16. Trephination was the only surgical procedure performed on 4 patients in whom membranes were not seen and on 7 in whom membranes were observed but not excised. Craniotomy was performed on 12 patients most of whom had been initially examined through burr holes. In 1 patient on whom trephination had not been carried out no membranes were found at craniotomy. In the remaining 10 patients membranes were found and removed.

Table VIII. Follow-up and abnormalities observed*

	Effusion	*No effusion*
Total followed	59	28
Died	10	5†
Recovered without apparent abnormality	34	15
Alive with residua	15	8
Intelligence		
Severely impaired	4	2
Moderately impaired	7	2
Normal	38	19
Behavior disorder	2	1
Convulsions	8	1
Neurological sequelae		
Mild	3	2
Severe	4	1

*Intelligence levels were tested in some patients and approximated clinically in others. The severely retarded group generally conforms to the I.Q. level of less than 60; and the moderate, between 60 and 80. Severe neurological abnormalities included lesions such as hemiplegia, monoplegia, and blindness; an isolated positive Babinski sign is representative of the mild abnormalities.

†A sixth patient died of hydrocephalus 1½ years after the acute illness.

Table IX. Follow-up electroencephalography

Result of EEG	*Subdural effusions*	*No subdural effusions*
Voltage asymmetry alone	9	3
Seizure discharges alone	4	1
Both voltage asymmetry and seizure discharges	1	1
Normal	27	14
Total	41	19

Part II. Follow-up examination.

Clinical evaluation. The results of the follow-up clinical examinations are listed in Table IX. The total number of patients with residua and the number of patients who apparently escaped residua are indicated in the top portion of the table and the incidence of the various defects noted is indicated at the bottom. It is striking that 56 per cent of these patients appeared to be normal at the time of follow-up examination. Of those who survived the acute illness 32 per cent were found to have some evidence of damage to the central nervous system. In these respects the patients with subdural effusions did not differ significantly from those without effusions. The incidence of persistent convulsions was somewhat greater in the group of patients who had had effusions. Prognosis was not significantly different statistically in patients whose effusions were found following routine taps than in those who had had specific indications for the tap.

Electroencephalography. Electroencephalography was carried out at follow-up examination in 60 patients, of whom 41 had had effusions and 19 had not (Table IX). Seizure discharges, voltage asymmetry, or both were present in approximately 30 per cent

of each group and differences between the 2 groups were not significant. Follow-up electroencephalograms were obtained in 2 patients with effusions in whom asymmetry of voltage was found at the time of the acute meningitis. In 1 of these, the asymmetry was still present 8 years later, whereas in the other a normal electroencephalogram was obtained at follow-up. Of those with normal electroencephalograms during the acute illness, 1 had asymmetry at follow-up and 4 had normal records. The electroencephalogram was normal at follow-up in only 3 of 9 patients with persistent convulsions in whom the examination was performed, whereas 38 of 52 patients without seizures had normal follow-up electroencephalograms. Follow-up roentgenographic examination of the skull was carried out in only 5 patients, 4 of whom had had subdural effusions. In 1 of these patients, in whom membranes had been seen but not removed, calcification was observed in the area of the previous effusions.[24]

Communicative behavior. Examination of hearing and speech (Table X) were carried out in 43 patients who had had effusions and in 18 controls. Communicative disorder

Table X. Abnormalities of hearing and speech

	Effusion	*No effusion*
Hearing defect	2*	0
Speech defects		
Articulatory problem	2	1
Articulatory problem and delayed speech	1	1
Articulatory problem and limited language comprehension	1	0
Delayed speech	1	1
Total tested	43	18

*One peripheral nerve hearing impairment (hypoacusis) and 1 central auditory disorder (dysacusis).

Table XI. Influence of aspects of the acute meningitis on condition at follow-up

	Positive taps			*Negative taps*		
	Dead	*Alive with residua*	*No sequelae*	*Dead*	*Alive with residua*	*No sequelae*
Total	10	15	34	5	8	15
Organism						
H. influenzae	4	8	15	5	3	5
Pneumococcus	5	5	9	0	1	0
Meningococcus	0	0	5	0	2	3
Other	0	1	1	0	1	3
Not recovered	1	1	4	0	1	4
Age at onset						
0 to 6 months	6	6	12	2	3	10
7 to 12 months	3	9	15	2	3	4
13 to 18 months	1	0	6	1	1	1
19 to 24 months	0	0	1	0	0	0
Over 4 years	0	0	0	0	1	0
Duration before treatment						
Under 24 hours	1	2	11	2	1	7
1 to 4 days	6	8	14	0	3	5
Over 4 days	3	5	9	3	4	3
Onset with						
Coma	3	4	3	3	3	0
Convulsions	4	5	12	2	3	0
Neurological signs	2	4	4	2	5	0

of some type was found in 10 of these patients. The incidence of such disorders in patients with effusions did not appear to be significantly different from that observed in controls. There were only 2 children with auditory problems, in 1 of whom a mild peripheral nerve hearing loss may have been unrelated to meningitis. The other had a central auditory disorder, severe language disorder, and general psychomotor retardation. Among the speech problems there were 6 articulatory abnormalities; the other 2 demonstrated delayed speech.

RELATION OF DETAILS OF THE ACUTE ILLNESS TO CONDITION AT FOLLOW-UP

The relationships between certain aspects of the acute purulent meningitis and the ultimate outcome are shown in Table XI. Patients with meningococcal meningitis appeared to have a better prognosis than those with disease due to other organisms but differences in outcome among the groups with different infecting organisms were not statistically significant. Most of the patients with and without effusions were less than 1 year of age, but there did not seem to be significant differences in the incidence of death or sequelae that could be related to the age at onset. Patients in whom the duration of symptoms before the institution of adequate antibacterial therapy was less than 24 hours had a considerably lower incidence of mortality and sequelae than did patients with longer durations. However, there were no differences between the groups of patients with and without effusions in this respect. The presence of coma, convulsions, or serious neurological abnormalities at the onset of the initial episode of meningitis was associated with a poor prognosis. Except in patients presenting with convulsions, the presence or absence of effusions did not appear to influence the prognosis. Convulsions at onset in patients with effusions were followed by death or residua in 43 per cent of instances. Onset with convulsions in those without effusions, and onset with coma or neurologic findings in both groups led to death or sequelae in 60 to 100 per cent of patients.

Character of the effusion and outcome. The relationships between certain details of the character of the effusion and the ultimate outcome are presented in Table XII.

Table XII. Details of the subdural effusion and outcome

	Total No. of patients	*Died*	*Alive with residua*	*Escaped clinical sequelae*
Duration of effusion				
Over 15 days before dry (by taps or surgery)	24	1	9	14
Under 15 days before dry	18	0	4	14
Size of effusion (maximum volume removed at any single subdural tap)				
Under 15 ml.	25	7	3	15
15 to 30 ml.	7	1	2	4
30 to 40 ml.	9	0	2	7
40 and over	18	0	8	10
60 and over	10	0	7	3
Nature of the fluid				
Clear	2	1	0	1
Xanthochromic and bloody	44	4	11	29
Purulent	4	3	0	1
Purulent and xanthochromic or bloody	9	2	4	3
Organism cultured from the subdural fluid	4	2	1	1

Sequelae were more common in patients in whom effusions were present for long periods of time. Seventy-eight per cent of those in whom the duration of effusion was less than 15 days appeared normal at the time of follow-up, and only 2 of those who appeared normal had abnormal electroencephalograms. The only patient with severe residua in this group had prolonged, untreated hyponatremia at the time of the acute meningitis.[25] In those in whom the duration of effusion was over 15 days, 58 per cent appeared to have escaped sequelae but, of these, 36 per cent of the patients in whom electroencephalography was performed had abnormal tracings. The size of the effusion also appeared to influence the prognosis since 60 per cent of those in whom volumes of over 15 ml. were never obtained on subdural tap escaped clinical sequelae, while 70 per cent of those in whom volumes of greater than 60 ml. were obtained had obvious residua. The number of patients in whom the infecting organism was cultured from the subdural fluid was too small to permit adequate evaluation of this factor, but 2 of these 4 patients died and 1 had clinical evidence of sequelae. Similarly 3 of 4 patients in whom the subdural fluid was purulent died, and a poor prognosis was also associated with the presence of subdural fluid containing purulent material admixed with bloody or xanthochromic fluid.

Treatment and outcome. The relation between local treatment of the effusions and the outcome is presented in Table XIII. Follow-up data were available for 16 patients in whom subdural membranes were seen. In 9 of them the membranes were excised, while in the other 7 they were left in situ. The rationale for the latter procedure was not given but it permits an interesting comparison. Of the 9 patients in whom membranes were removed surgically, 7 were found to be entirely without clinical sequelae. One patient should be excluded from comparison for he received grossly inadequate antibacterial therapy for pneumococcal meningitis. Thus, 7 of 8 patients appeared to have escaped permanent sequelae and the remaining patient had bilateral Babinski responses but was otherwise unaffected. Electroencephalograms were carried out on 6 of the 7 clinically normal patients in whom membranes were removed and were abnormal in 2. Results were notably worse in the 7 patients whose membranes were not excised. Five were found to have clinical evidence of central nervous system disease. Of 2 who appeared to have escaped sequelae, electroencephalography was performed in 1 and found to be abnormal. An additional patient in whom trephination failed to reveal an anterior subdural effusion died shortly after subsidence of the acute infection.

In the group of patients treated by repeated subdural taps without surgical exploration, it is possible to compare those in whom taps were continued until the subdural space appeared dry with those in whom treatment was terminated before this situation was achieved. There were follow-up data for 25 patients in the former group and 7 in the latter after excluding 2 patients from the former group and 4 from the latter who died before adequate treatment of the initial meningitis could be carried out. Seventy-two per cent of those tapped until dry were without clinical evidence of sequelae, and electroencephalography which was performed on 17 of these 18 patients was normal in 14. On the other hand, in the other group 4 of 7 appeared clinically to be without residua, and, among these 4, 2 of the 3 electroencephalograms performed were abnormal. The better prognosis observed in the group in which negative subdural taps were the criteria for termination of therapy was not significant statistically but the numbers are small and it seems intuitively consistent. The 2 deaths among the 7 patients in whom dry taps were not ascertained occurred 3 and 37 days after discharge and were not explained, while the single late death among the 25 in the other group followed a second attack of pneumococcal meningitis.

Inasmuch as the presence of coma, convulsions, or neurological abnormalities at

Table XIII. The effects of local treatment on outcome

Method of treatment	*No. of patients*	*Not followed*	*Died*	*No. of patients alive with residua*	*No. of patients recovery without sequelae*
Drainage by subdural taps					
Volume of fluid at last tap:					
Under 1.0 ml.	33	6	3*	6	18
Over 1.0 ml.	12	1	6†	1	4
Subdural taps and trephination without craniotomy					
Subdural membrane:					
Not found	4	0	1‡	1	2
Present and left in situ	7	0	0	5	2
Craniotomy					
Subdural membrane:					
Absent	1	0	0	1	0
Excised	10	1	0	2§	7
Total	67	8	10	15	34

*Two of these died during the acute infection at 3 and 6 days, respectively. The third patient died after recovery from a second attack of pneumococcal meningitis and at the time of death subdural taps were negative as was the cerebrospinal fluid.

†Four died before treatment could be completed. The other 2 died 3 and 37 days after discharge, respectively; in the former, autopsy was not performed and, in the latter, this examination did not reveal the cause of death.

‡Autopsy revealed an anteriorly situated subdural effusion, not visible from the burr holes.

§One patient had inadequately treated pneumococcal meningitis.

the onset of acute meningitis was associated with a relatively poorer prognosis than when these clinical features were absent, it was of interest to determine the influence of these features in patients in whom different methods of treatment were employed. Of those in whom membranes were found and excised one or more of these features was present at onset in 5 patients, 4 of whom recovered without sequelae; in 4 patients in whom these factors were absent, 3 escaped neurological sequelae, and 1 patient had an isolated weakness of extraocular movements. Among the patients in whom membranes were seen and left in situ, sequelae were present in all 3 in whom these features were present at onset, and in 2 out of 4 in whom they had been absent.

DISCUSSION

The incidence of subdural effusions complicating purulent meningitis is of clinical importance as it influences therapeutic management of meningitis. The relatively low incidence of this complication (6 to 17 per cent) presented in some series[14, 16-18] implies that effusions are relatively infrequent complications producing unequivocal, easily detectable clinical manifestations. On the other hand, an incidence of over 50 per cent as reported by McKay, Ingraham, and Matson[4] and by Smith, Dormont, and Prather[8] suggests a more vigorous search for the complication. That the incidence of effusions may be related to the vigor with which they are sought is suggested by the data of the present series in which the 67 patients found to have subdural effusions were 21 per cent of the total 320 patients with purulent meningitis seen during the period of study, but they represented 62 per cent of the patients in whom taps were performed. The fact that 34 per cent of the subdural effusions in this series were discovered in the process of routine taps indicates the advantages of routinely tapping the subdural space in patients with purulent meningitis as well as the inadequacies of currently employed in-

dications for this procedure. Since 80 per cent of the patients with and without effusions were less than 12 months of age and effusions were sought in only 4 patients over 18 months of age, data are not sufficient to permit evaluation of the indications for search for effusions in patients in whom the fontanel is closed. Electroencephalographic changes may suggest the presence of an effusion but the data do not support the recommendation[26] that a negative electroencephalogram warrants a conservative approach. The possibility that the trauma of an initial subdural tap might induce iatrogenic subdural hematomas has been suggested as an argument against the routine performance of subdural taps.[17] In this series 78 per cent of the effusions were detected on the first subdural tap. Moreover, the observation that the frequency of previous negative subdural taps was greater in patients without effusions than in those with effusions is further evidence against this possibility. A similar observation was made by Platou and associates.[14]

Meningitis was due to *Hemophilus influenzae* more commonly than to any other organism, and this organism was found with equal frequency in patients with and without effusions. Patients with pneumococcal meningitis, however, appeared to have an increased likelihood of effusions while meningococcal meningitis was less commonly associated with effusions.

The predominance of males and of Negro infants in the group with effusions as compared with those without effusions is of interest and appears not to have been noted previously. The predominance of Negroes was greatest in patients with pneumococcal meningitis, but the predominance was general as was the greater incidence of males in the group with effusions.

It was of interest that over half the patients appeared to be normal at the time of follow-up examination. The patients with effusions did not differ from controls in this respect. The prognosis was worse in patients in whom the interval from the onset of symptoms to the institution of adequate therapy was greater than 24 hours and in whom coma, convulsions, or neurological findings were present at onset, but the patients with and without effusions did not differ in these respects. Sequelae were more common in patients in whom effusions were present for long periods of time, and in whom the volumes removed were large. This latter observation suggests that large effusions are associated with a relatively poor prognosis. It is also consistent with recommendations[4] that volumes greater than 15 to 20 ml. should not be removed at any single decompression. In this series, 1 patient had a focal left-sided convulsion immediately after the removal of 90 ml. of fluid from the right subdural space. Similarly, 1 patient with a bilateral effusion had 6 negative taps on 1 side, but 3 days after the last negative tap had a contralateral craniotomy for a large persistent effusion. On the following day, he developed a large persistent effusion on the previously negative side.

Changes in methods and philosophy of management of subdural effusions over the years studied permit the evaluation of a number of different methods of therapy. Even in a relatively large series the number of patients in any of these therapeutic categories is small, but certain inferences seem readily made from the data. Answers to some of the therapeutic questions could be obtained more definitely by a carefully controlled alternated prospective study. However, the weight of opinion is such that it is unlikely that such a study will ever be made. Therefore, fortuitous therapeutic experiments and early experiences gain added weight. Among patients in whom the only treatment was repeated subdural taps, the prognosis appeared to be better in those in whom evidence of a dry subdural space was the indication for the termination of therapy. It was also possible to evaluate the long-term results of therapy in 2 groups of patients in whom subdural membranes were seen. The fact that there are 2 groups suggests that some of those in whom the membranes were excised may have had more severe initial disease, as does the fact that

the incidence of manifestations at onset which were associated with a poor prognosis were more common in the group in which membranes were removed. However, the patients in whom membranes were seen and not removed had a markedly poorer ultimate outcome than those in whom the membranes were removed. These data suggest that in the presence of effusion a dry subdural space should be the indication for termination of drainage by subdural taps, that volumes of fluid in excess of 15 to 30 ml. should not be removed at any single subdural tap, and that further investigation by trephination should be carried out if subdural taps continue to yield fluid readily after 2 weeks of repeated drainage. Subdural neomembranes, when found, should be excised.

SUMMARY

Patients in whom subdural effusions complicated acute purulent meningitis and a control group in whom subdural taps were negative were investigated for the presence of clinical and developmental abnormalities at follow-up. More than 50 per cent of the patients were examined more than 4 years after the acute meningitis. In the majority of instances meningitis was caused by *Hemophilus influenzae,* but this organism was not found more frequently in patients with effusions than in the controls. Patients with pneumococcal meningitis appeared more likely and those with meningococcal meningitis less likely to develop subdural effusions than not. There was a predominance of males and of Negroes in the group with effusions, which was not found in the control group.

A relatively poor prognosis was associated with the presence of coma, convulsions, or neurological abnormalities at the onset of the acute meningitis. This was true in the presence or in the absence of effusions. Among those with effusions permanent sequelae tended to be more frequent in those in whom effusions were large and present for long periods of time. In patients treated with subdural taps alone prognosis was better when the indication for termination of therapy was evidence of a dry subdural space than when drainage was discontinued earlier. Patients in whom membranes were seen and excised did very well in spite of the presence of previously stormy courses, while those in whom membranes were seen and not removed had a high incidence of permanent sequelae.

We gratefully acknowledge the assistance of Mr. Joseph Dallas, who expertly traced a number of missing patients and made them available for follow-up examinations. The electroencephalograms were read by Dr. Curtis Marshall.

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Diagnosis of enteropathogenic E. coli diarrhea by fluorescein-labeled antibodies

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ENTEROPATHOGENIC *Escherichia coli* are an important cause of diarrhea of infancy. Although the majority of the 140 or more known serotypes of this organism are presumably innocuous in the gastrointestinal tract, the pathogenicity of at least ten of the serotypes has been well established by numerous investigators.[1] Whitaker and co-workers[2] used the fluorescent antibody technique to identify a single pathogenic serotype ($0127:B_8$) of *E. Coli* in stool specimens obtained from a nursery outbreak of diarrhea and found it superior to cultural methods. The present study was instituted in an attempt to use fluorescein-labeled, type-specific antisera against 10 known serotypes of enteropathogenic *E. coli* for rapid diagnosis of enteropathogenic *E. coli* infection.

The incidence of enteropathogenic *E. coli* infection in many people's experience is greater than that of salmonellosis and shigellosis. Quilligan and Shadomy[3] found 36 cases of enteropathogenic *E. coli* infection in 106 infants with diarrhea. Herweg and colleagues[4] reported enteropathogenic *E. coli* infection in 50 cases out of 123 infants with diarrhea from St. Louis Children's Hospital. In a study of 466 infants with gastroenteritis, Derham and Rogerson[5] found that 144 were due to pathogenic serotypes of *E. coli*, 97 to Shigella, and 30 to Salmonella.

Because of the absence of characteristic clinical signs or symptoms of this disease compared with the many other causes of diarrhea in infancy, the diagnosis is based entirely on isolation of a known pathogenic serotype of *E. coli* by culture and agglutination methods.

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This study was supported in part by grants from the Dallas Foundation and Wyeth Laboratories.

**This investigation was carried out in part during the tenure of a Postdoctoral Fellowship from the National Institute of Allergy and Infectious Diseases, United States Public Health Service.*

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METHODS AND MATERIALS

Preparation and conjugation of antisera. Type-specific antisera were prepared by inoculation of rabbits with suspensions of the O antigens of 10 pathogenic serotypes of *E. coli** (026:B6, 055:B5, 086:B7, 0111:B4, 0119:B14, 0124:B17, 0125:B15, 0126:B16, 0127:B8, and 0128:B12). The globulin fractions of the antisera were conjugated with fluorescein isothiocyanate by the method of Riggs.[6] This method consists of salting out the globulin fraction of the serum by adding by drops an equal volume of 4 molar ammonium sulfate. The material is kept overnight in the refrigerator and then centrifuged and washed with 1.75 molar ammonium sulfate. After recentrifugation the sediment is suspended in a volume of phosphate-buffered saline (pH 7.2 to 7.4) equal to the original volume of serum. Dialysis against buffered saline is carried out for from 24 to 48 hours to remove the ammonium sulfate. The protein content of the material is determined by the Biuret or micro-Kjeldahl method and adjusted to 10 mg. per milliliter by dilution with buffered saline and 10 per cent carbonate-bicarbonate buffer (pH 9). Fluorescein isothiocyanate is added in the amount of 0.05 mg. for each milligram of protein. The material is placed on a magnetic stirrer for from 24 to 48 hours to allow the dye to go into solution. Then the conjugated antiserum is dialyzed against frequent changes of buffered saline until all the excess fluorescein has been removed. (This usually requires from 5 to 7 days.) All the steps are carried out in a cold room and refrigerated centrifuge and the solutions used must be cold (4° C.).

The conjugated antiserum may be absorbed with liver powder or Dowex to diminish nonspecific staining. In some instances the authors have obtained better results using a final protein concentration of from 20 to 50 mg. per milliliter rather than the 10 mg. per milliliter indicated by Riggs.

Specificity was established by testing each individual type of antiserum for fluorescent staining with all types of enteropathogenic *E. coli*, many nonpathogenic *E. coli*, *E. freundii*, various Shigella and Salmonella, species of Proteus, *Aerobacter aerogenes*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Alcaligenes fecalis*, providence and arizona groups, *Streptococcus fecalis*, Group A streptococci, pneumococci, *Bacillus pertussis*, staphylococci, and *Candida albicans*. Cross-staining was infrequently encountered; it was of low intensity and could always be eliminated by adsorption of the fluorescent antiserum with the appropriate organism.

Clinical material. The patients studied consisted of a group of 165 children under 2 years of age hospitalized for diarrheal disease during a 7-month period in 1959 to 1960 and a second group of 210 clinic patients under 2 years of age seen in the outpatient department for a chief complaint of diarrhea.

Two rectal swabs were obtained from each patient. One was used for inoculation of eosin methylthionine chloride, Salmonella-Shigella, and blood agar plates and tetrathionate broth. After 18 hours subcultures were made on Salmonella-Shigella agar from the tetrathionate broth. Biochemical tests on triple sugar-iron agar, Simmon's citrate, and urea agar were performed together with appropriate serologic tests for the identification of pathogenic organisms.

The second swab, moistened with a small amount of sterile normal saline, was used to smear a small area in the center of several microscope slides for use in the fluorescent antibody test. One or more follow-up specimens were obtained from each outpatient and daily rectal swabs were taken from the hospitalized babies for further examination by fluorescent staining.

Examination of specimens. The slides were fixed in acetone, stained with 1 drop of fluorescein-labeled antiserum for 30 minutes, and mounted in glycerol under a cover slip. The microscope employed was a Reichert with a dark-field condenser illuminated by a 250-watt mercury arc lamp with appropriate filters.

*Stock cultures were supplied by Dr. Wm. W. Ferguson of the Michigan Department of Health, Lansing, Mich.

Table I. Results of bacteriologic and fluorescent antibody examination of rectal swab specimens from infants with diarrhea

Study group	*Total no. of patients*	*Patients positive by bacteriologic method*						*Patients positive by fluorescent antibody method*	
		Shigella		*Salmonella*		*Enteropathogenic E. coli.*		*Enteropathogenic E. coli.*	
		No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
Hospitalized infants	165	15	9.1	7	4.3	26	15.8	32	19.4
Outpatient infants	210	26	12.4	1	0.5	13	6.2	15	7.1
Total	375	41	10.9	8	2.1	39	10.4	47	12.5

As an initial screening test 3 pools were made from the separate antisera, and specimens were stained with them. If positive fluorescent organisms were detected in one of the pools, further staining was then done with the individual antisera comprising that pool to determine the specific type of enteropathogenic *E. coli* present in the specimen.

Positive fluorescence was graded by both intensity of staining and numbers of organisms present. The intensity was:

4+, brilliant apple-green fluorescence with "halo,"
3+, bright apple-green fluorescence with "halo,"
2+, dim green fluorescence without "halo,"
1+, faintly detectable green color; and
0, no fluorescence or blue-white autofluorescence.

Only fluorescence of 3 to 4+ intensity was considered significant. Cross-staining, when it was present, was never more than 1 to 2+ intensity.

The number of organisms was:

4+, masses of organisms in every field;
3+, 10 to 50 organisms in every field and occasional clumps;
2+, 2 to 10 organisms in every field;
1+, 0 to 2 organisms in every field; and
0, no organisms seen.

RESULTS

Results of cultural methods. Results of the bacteriologic examination of all patients are given in Table I. Among the hospitalized infants pathogenic serotypes of *E. coli* were found more frequently than were Salmonella and Shigella combined (15.8 per cent versus 13.4 per cent, respectively). *Shigella flexneri* or *Shigella sonnei* were the most common pathogens isolated from the clinical group of patients (12.4 per cent). This is in accord with the authors' experience that shigellosis is a very common infection in the Dallas area and that the majority of cases are not severe enough to require hospitalization, whereas enteric infections with Salmonella species and enteropathogenic *E. coli* tend to be more protracted in their course and more severe in their manifestations.

Results of fluorescent antibody examination. The results of fluorescent antibody examination of rectal swabs are also given in Table I. The most frequently encountered serotypes were *E. coli* 0119 and 055; the other serotypes occurred with approximately equal frequency.

The number of organisms seen on the specimens appeared to vary in proportion to the amount of fecal material present; therefore, the number of organisms did not necessarily reflect the severity of the disease. If a measured amount of stool had been used instead of a rectal swab, the quantitation of fluorescent organisms might have been found to correlate with the severity of the infection.

Fluorescent antibody staining versus cultural examination. There were some discrepancies encountered in the results ob-

tained by the two tests. Forty-seven patients had enteropathogenic *E. coli* infection by fluorescent antibody examination but only 39 cases were detected by agglutination of culture and slide.

The original organism isolated and/or a frozen stool specimen obtained at the initial examination were saved to be restudied in all but 10 of the cases. When there was a difference in the results by the two methods, these specimens were re-examined by agglutination and by fluorescent staining of the culture.

The comparative results are presented in Table II. In 316 cases both tests were negative for the presence of pathogenic serotypes of *E. coli* and in 27 cases there were positive results by fluorescent staining and by reactions from agglutination of the initial culture.

In 15 instances the results of the fluorescent antibody test led to the discovery that the original culture report was erroneous. In 8 cases the culture was reported negative but the fluorescent antibody test was positive. On re-examination subcultures of the originally isolated organisms were found to be a pathogenic serotype by both agglutination and fluorescent staining. The reverse situation was encountered in 7 cases, i.e., a culture originally reported as positive was found to be negative when restudied.

These cultural errors were due in some cases to overgrowth of the pathogenic *E. coli* by nonpathogenic organisms. In other cases *E. coli* were isolated but they either failed to cause agglutination or there was clumping of the suspension of organisms following heating at 100° C. for 30 minutes that interfered with the slide agglutination test. In addition, the commercial typing antisera for enteropathogenic *E. coli* are of low titer and this sometimes results in agglutination so weak or delayed that it may be overlooked. Antibiotics administered before the cultures were taken might reduce the number of viable organisms, making it difficult to identify them by culture.

Fluorescent staining is not dependent on the viability of the organism, as has been suggested previously by Whitaker and coworkers.[2] By fluorescent staining of cultures killed by Formalin the authors have observed that nonviable organisms exhibit less brilliant fluorescence, tend to form rather amorphic aggregates, and have a distorted morphologic condition with irregular cellular outlines and small coccoid forms. "Healthy" organisms, on the other hand, appear distinctly outlined even when present in great numbers in a specimen.

In 5 cases the diagnosis of an enteropathogenic *E. coli* infection was missed by the fluorescent antibody test. This was in all likelihood due to the fact that some of the rectal swabs had little or no fecal matter on them. If stool specimens were used for study instead of rectal swabs, this difficulty should be avoided. One practical disadvantage of using stool specimens is that one may have to wait several hours for the patient to pass a stool even in cases of diarrhea.

Confirmation of a positive fluorescent antibody result could not be obtained by culture in 2 cases. Since the fluorescent antisera were proved to be highly specific by extensive testing for cross-staining, these cases are considered to represent a failure of the culture method.

Table II. Comparison of detection of enteropathogenic *E. coli* by culture and fluorescent antibody methods in 375 cases of diarrhea*

	Original culture	*Re-examination of culture or frozen stool specimen*	*Fluorescent antibody staining tests*	*Number*
Tests agree	−	−	−	316
	+	+	+	27
	−	+	+	8
	+	−	−	7
Tests do not agree	+	+	−	5
	−	−	+	2
Inadequate material for restudy				10
				375

*+ = positive results, − = negative results.

Effect of antibiotic therapy on fluorescent morphology. By fluorescent staining of daily rectal swab specimens obtained during treatment with neomycin, quantitative and qualitative changes in the pathogenic *E. coli* were observed. In all instances, there was a marked decrease in the number of organisms present in 24 hours; the bacteria appeared smaller, the cellular outline was less distinct, and the brilliant halo appearance of fluorescence was lost. By from 48 to 72 hours only amorphous clumps of distorted bacteria were found. After that period of time no recognizable antigenic material was present in the stool. Pathogenic organisms could not be isolated by culture after 24 hours of neomycin therapy except in 1 patient who became an asymptomatic carrier of *E. coli* 055:B5 for 2 weeks when treated with 50 mg. of neomycin per kilogram per day. When the dosage of the antibiotic was increased to 100 mg. per kilogram per day, the microorganism disappeared. No other carriers were detected.

These morphologic alterations are almost identical with those mentioned previously in regard to fluorescent staining of organisms killed with Formalin.

CONCLUSIONS AND SUMMARY

The fluorescent antibody test is a rapid and reliable method for the detection of enteropathogenic *Escherichia coli* in rectal swab specimens. Cross-staining with other pathogenic and nonpathogenic organisms does not cause difficulty in interpreting the results of fluorescence.

Previously administered antibiotics may inhibit cultural growth but they do not eliminate fluorescent staining.

The fluorescent antibody test is superior to standard bacteriologic methods in rapidity, economy, simplicity, and in the detection of a greater number of patients with enteropathogenic *E. coli* infection.

The authors are grateful to Berenice Thomason of the Communicable Disease Center, Atlanta, for confirming the results of agglutination and fluorescent staining of cultures in which there was disagreement between the two methods of examination.

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Vitamin B_{12} deficiency associated with disease of the small intestine

Observations on an infant following extensive small bowel resection

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AMONG nutritional anemias encountered in infancy and childhood the microcytic, hypochromic anemia of iron deficiency is the most common. The less frequent megaloblastic anemia is usually a result of dietary deficiency and responds specifically to treatment with folic acid.[1] Megaloblastic anemia may also be due to a vitamin B_{12} deficiency which is almost invariably associated with either a defect of intrinsic factor or with structural abnormalities of the small intestine. The vitamin B_{12} deficiency associated with disease of the small intestine may be a complication of previous surgery, but surgical relief of intestinal stasis can also relieve B_{12} deficiency. In other cases, deficient ileal absorption of the vitamin is improved by medical treatment of an intestinal disease or is compensated for by periodic vitamin B_{12} injections. We have had the opportunity to observe a patient who illustrates the association of vitamin B_{12} deficiency with disease of the small intestine and who provides a background for a discussion of the condition.

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This study was supported by Grant No. HTS-5255 from the National Institutes of Health and by the John A. Hartford Foundation.

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CASE REPORT

The patient was the product of a pregnancy complicated by toxemia in the third trimester. The delivery was precipitate but resuscitation was not necessary. The birth weight was 5 pounds, 3 ounces. At 36 hours of age the infant was admitted to The Children's Hospital Medical Center with vomiting and abdominal distention. Markedly enlarged jejunal loops of bowel on x-ray examination were declared consistent with intestinal atresia. Laparotomy revealed a thin-walled cystic segment of bowel containing 400 c.c. of green fluid, filled proximally by the jejunum and connected distally by a solid cord to a short pouch of terminal ileum. The resection included bowel from a point 8 inches below the ligament of Treitz to the middle of the ascending colon. Pathologic section proximally showed jejunal mucosa. The postoperative course was complicated by acidosis, tetany and dehy-

dration with an average of 25 bowel movements per day. Several apneic episodes are recorded and convulsions were noted following one of these. The birth weight was not regained until 7 weeks of age.

The patient had 3 further admissions with acidosis and dehydration between 3 and 5 months of age. Cataracts, assumed to be congenital, were noted. Several small blood transfusions were given for anemia. He was subsequently followed at home by his family doctor. He remained below the third percentile for height and weight. At 15 months of age his weight was 17 pounds. He tolerated a low-fat formula and a variety of strained foods and produced only 2 or 3 loose to watery bowel movements per day. He did not visit the clinic again until he was 2 years, 11 months of age. Cataracts had recently been removed at another hospital. In the interval, he had had recurrent diarrhea and little evidence of mental or physical development, as at the age of 1 year, he could sit only with support. He was said to have had an anemia at age 1½ which responded to therapy with an unknown oral hematinic after failure with intramuscular iron. During the 5 months following this clinic visit the patient developed increasing irritability, pallor, anorexia, and more frequent bowel movements.

At 3 years, 4 months of age he was admitted with a mild upper respiratory infection, marked pallor, and dehydration. Physical examination revealed a markedly retarded child with weight of 17 pounds, 6 ounces, pulse 160, and respiratory rate 40. He was unable to sit without support and he could not speak. Subcutaneous fat was minimal and the tissue turgor was poor. The eyes revealed iridectomies, rotary nystagmus, and strabismus. The pharynx was minimally injected. No glossitis was noted. There were hypermobility and hyperextensibility of the joints of the extremities. Deep tendon reflexes were normal.

Laboratory findings were: hemoglobin 4.0 Gm. per cent; hematocrit 15.5 per cent; erythrocyte count 1.35 million per cubic millimeter; mean corpuscular volume 115 cubic microns; mean corpuscular hemoglobin 29.6 γγ; mean corpuscular hemoglobin concentration 25.8 per cent; platelets 48,000 per cubic millimeter; and white blood count 6,600 per cubic millimeter.

Differential count was: polymorphonuclear leukocytes 24; band forms 18; eosinophils 2; lymphocytes 50; atypical lymphocytes 3; monocytes 3; and 2 nucleated red blood cells per 100 white blood cells. Neutrophils contained hypersegmented nuclei; there was anisocytosis; about 20 per cent of the red cells were macrocytic.

Bone marrow analysis showed: proerythroblasts 28 per cent; erythroblasts 21 per cent; and normoblasts 24 per cent. About 40 per cent of erythrocyte precursors revealed megaloblastic changes. Megakaryocytes were decreased. Many myelocytes and metamyelocytes were enlarged. The serum iron was 115 μg per cent; serum folic acid (activity) 37.8 mμg per milliliter (normal 7 to 24+)*; serum vitamin B_{12} 49.0 μμg per milliliter (normal 200 to 900)*; serum vitamin C 0.62 mg. per cent (normal 0.4 to 1.5 mg. per cent); glucose tolerance test, oral: fasting blood sugar 77 mg. per cent, ½ hour 123, 1 hour 120, 2 hours 116, and 3 hours 108; vitamin A absorption, fasting level 17.8 μg per cent, 5 hours 169 μg; gastric juice, free acid without histamine stimulation; stool fat 2.8 Gm. per day (normal below 3.9 Gm. per day on a normal diet); intestinal transit time as measured with a carmine marker 7 hours and 19 hours (normal 20 to 48 hours); and upper gastrointestinal series and barium enema revealed no stasis of bowel content.

Clinical course. The patient was rehydrated with intravenous fluids and specific therapy for the anemia was initiated with intramuscular vitamin B_{12}, 1 μg per day. After 6 days a reticulocyte peak of 23.7 per cent was obtained (Fig. 1), and after 9 days the platelet count returned to normal. After 17 days of therapy serum iron had dropped to 37 μg per cent. Bone marrow aspiration after 3 days of therapy showed

*We are grateful to Dr. Victor Herbert of the Thorndike Laboratory, Boston City Hospital, for these determinations.

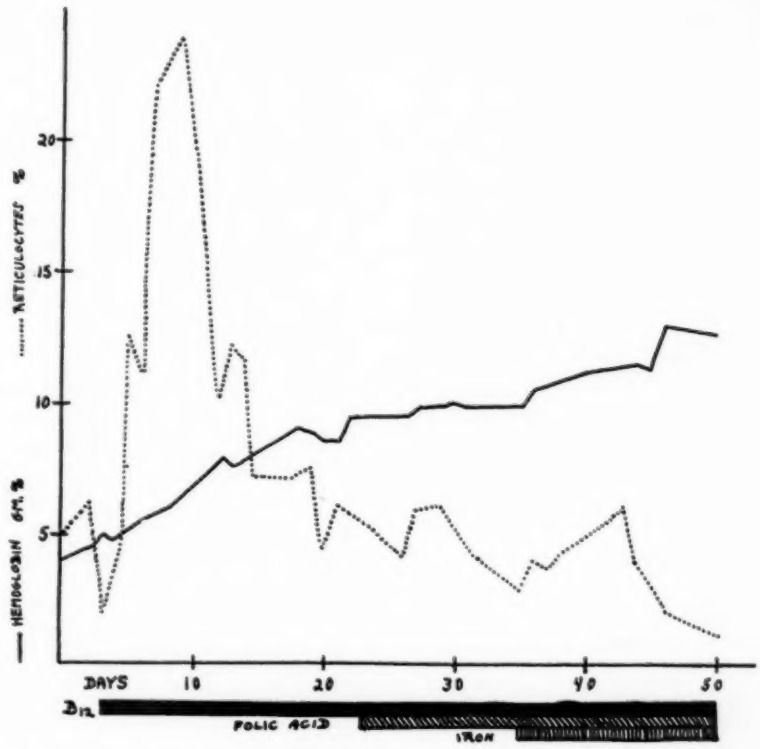

Fig. 1. Hemoglobin and reticulocyte response to vitamin B_{12}, folic acid, and ferrous sulfate.

fewer megaloblastic elements and greater maturation of the erythroid series. After 9 days the marrow cells were normal in appearance. The erythroid/myeloid ratio of 1/1 and 45 per cent normoblasts indicated active erythropoiesis. The hemoglobin rise averaged 0.2 Gm. per cent per day over a period of 18 days. Appetite and responsiveness improved. After 18 days of vitamin B_{12} therapy alone, folic acid 0.2 mg. intramuscularly per day was added but provoked no definite additional reticulocyte response and no hemoglobin rise. After 13 days of this combined therapy, ferrous sulfate, 750 mg. per day orally (150 mg. elemental iron per day), was added to the regimen, and an additional reticulocyte response and hemoglobin rise were obtained. A rise of 0.2 Gm. per cent per day over the subsequent 14 days brought hemoglobin values into the normal range. Schilling tests* at this time and following 5 days of Achromycin therapy, 400 mg. per day, showed less than 1 per cent intestinal absorption of B_{12}. Since discharge from the hospital the patient has shown an accelerated growth and weight gain. He sits without support and crawls more actively, and has maintained good hemoglobin levels on ferrous sulfate, 500 mg. per day, and vitamin B_{12} therapy, 500 μg intramuscularly per month.

DISCUSSION

This case illustrates a B_{12} deficiency due to removal of the vitamin's major absorp-

*We are indebted to Dr. F. H. Gardner of the Peter Bent Brigham Hospital, Boston, Mass., for these determinations.

tive site, by a massive lower small intestinal resection. Small doses of vitamin B_{12} and folic acid were used as these permit better delineation of mixed deficiencies.[2, 3] A vitamin B_{12} deficiency was clearly demonstrated by the low level of serum B_{12}, less than 1 per cent intestinal absorption of the vitamin as demonstrated by the Schilling test, and a dramatic response to a low intramuscular dose of B_{12}. Serum iron was initially elevated as is characteristic in cases of megaloblastic anemia due to either folic acid or B_{12} deficiency even if an iron deficiency coexists. The drop of iron to subnormal levels is characteristic of a response to the appropriate agent.[4, 5] Serum folic acid activity[5] was initially in the high normal range, and no clinical evidence of response to this medication, given parenterally, was obtained. Stasis of intestinal contents was not demonstrated by x-ray studies, and therapy with Achromycin did not alter intestinal absorption of vitamin B_{12}. Since the deficiency of vitamin B_{12} developed as a result of absence of its major absorptive surface, the patient must continue to receive intramuscular vitamin B_{12} therapy.

The first description of pernicious anemia associated with intestinal stricture is attributed to Faber[6] who suggested that the anemia resulted from the absorption of a toxin from the stagnant bowel contents. In 1929, Meulengracht[7] collected 22 cases of this syndrome. Seven patients had tuberculosis of the small intestine or mesenteric lymph nodes. Two patients were cured of anemia, one by liver therapy and the other by resection of the area of stricture. The association of clinical pernicious anemia with a blind intestinal loop was recognized by Little[8] in 1929 in a young man who had had a series of operations for the repair of an intestinal fistula following acute appendicitis. The relative frequency of these two types of disease was indicated by Cameron, Watson, and Witts.[9] Of 61 cases (only 2 of which occurred in children) that they reviewed in 1949, 27 had strictures and 24 had fistulas or anastomoses leaving blind loops or pouches. Twenty-seven of the 61 cases were treated with liver extract, and in 22 a response was noted. These investigators also observed megaloblastic anemia in rats with surgically produced intestinal pouches designed to fill by peristalsis, especially if the pouches were created high in the small intestine.[10, 11] In man, also, diverticula located in the upper small intestine have been shown to be associated with megaloblastic anemia.[12–14]

In the past decade, the nature of the megaloblastic anemia due to intestinal stasis has been defined more precisely as a vitamin B_{12} deficiency by findings of subnormal serum vitamin B_{12}, decreased intestinal absorption of B_{12} as demonstrated by the Schilling test, and the hematologic response to intramuscular vitamin B_{12} therapy.[12–17] Stasis of intestinal contents and response of the anemia to treatment with antibiotics of the tetracycline group constitute a common denominator for cases of stricture, anastomoses, and diverticula. Presumably antibiotics function by altering the bacterial flora in the static bowel contents, destroying bacteria which consume vitamin B_{12} or, perhaps, aiding the growth of bacteria producing the vitamin.

In contrast to the anemia related to intestinal stasis, a deficient ileal absorptive surface appears responsible for vitamin B_{12} deficiency in patients with regional enteritis and other ileal disease, and in patients with massive ileal resections. The association of macrocytic anemia with regional enteritis was reported by Butt and Watkins[18] in 1936 and re-emphasized in 1957 by Meynell[15] and Cooke,[16] who observed that 42 of 80 patients with regional enteritis had low serum vitamin B_{12} levels. Impaired absorption was almost always restored with steroid therapy presumably in association with a decrease in ileal inflammation. In cases of massive ileal resection, megaloblastic anemia, low serum vitamin B_{12}, and low vitamin B_{12} absorption have been noted, but sometimes not until several years after operations.[17] It is rare that such cases respond to antibiotic therapy.[15, 17] Resection of the jejunum has not been found to interfere with B_{12} absorption.[17]

Idiopathic steatorrhea often presents a combined deficiency of folic acid and vitamin B_{12} and was associated with diminished serum vitamin B_{12} levels in 36 of 78 patients in one series.[14] The mechanisms underlying the deficiency in this condition are difficult to define, but many cases have responded to gluten-free diets.

INTESTINAL ABSORPTION OF VITAMIN B_{12}

Vitamin B_{12}, if provided in very large quantities, has been shown to be absorbed from oral and rectal mucosa as well as from the small intestine. At levels of normal intake, however, the ileum appears to be the major site of absorption in man. This is evident from the clinical data mentioned above and is corroborated by the results of recent studies by Booth and Mollin.[17] Four patients were studied at laparotomy 3 hours after an oral dose of 1 μg Co^{56} or Co^{58} labeled vitamin B_{12}. The radioactive material was found almost entirely in the distal small bowel while little or no radioactivity was yet present in the blood. As in normal subjects, peak plasma levels were found between 8 and 12 hours after the oral dose. It is interesting that the physiologic absorption of vitamin B_{12} should seem a specific function of the distal small intestine while most other nutriments are absorbed chiefly from the upper small intestine.

The effect of normal intestinal bacterial flora upon vitamin B_{12} supply is difficult to estimate. Most animals excrete more vitamin B_{12} than they take in their diets[19] and extracts of intestinal contents of horses have produced remissions in cases of pernicious anemia in humans.[20] In man, the amount of vitamin B^{12} in intestinal contents has been found slightly greater in the ileum than in the jejunum but much greater beyond the ileocecal valve.[20] Thus, much of the endogenous bacterially produced vitamin B_{12} does not seem available to the major absorptive site. The important role of exogenous vitamin B_{12} in man is demonstrated most clearly by cases of dietary vitamin B_{12} deficiency among vegetarians.[21]

It is not clear why stasis of intestinal contents produces vitamin B_{12} deficiency. Ungley[19] has discussed several possible mechanisms and the experimental evidence for each. It seems most likely that abnormal bacterial flora compete with the host for available vitamin B_{12}. The fish tapeworm is known to demonstrate such competition. The megaloblastic anemia produced by *Diphyllobothrium latum* will respond to elimination of the parasite, or, experimentally, to injection of the vitamin B_{12} rich extract of the worm.[22] Similarly the response of the megaloblastic anemia of intestinal stasis to treatment with the tetracycline group of antibiotics could be due to elimination of B_{12} consuming bacteria.

SUMMARY

Evidence is reviewed indicating that vitamin B_{12} is absorbed in the lower part of the small intestine in man. Cases of megaloblastic anemia related to intestinal disease are usually associated either with stasis of intestinal contents or with a defect in the absorptive function of the lower small intestine. The former group responds to therapy which relieves stasis or to broad-spectrum antibiotic treatment. The latter group responds to medical therapy improving the absorptive function of the affected bowel.

A case of megaloblastic anemia developing after a massive resection of small intestine in a newborn baby is presented. A case such as this requires long-term intramuscular therapy with vitamin B_{12}.

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Pulmonary changes in acute glomerulonephritis in childhood

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AT THE beginning of the year 1954, we observed 3 children with acute glomerulonephritis, who showed unexpectedly marked pulmonary changes on radiologic examination. At the time it was not clear whether these were a complication of the renal disease, a chance association, or part of the clinical pattern. It was therefore decided to make radiographs of the chests of every child with acute glomerulonephritis admitted to our hospital.

Forty children with acute nephritis were studied in a period of 3 years (1954 to 1957) and 25 of them had positive radiologic findings of varying nature and extent. These consisted in some of areas of segmental or even lobar collapse, in others of well-outlined or ill-defined shadows suggestive of consolidation, and only very rarely of pulmonary edema. These changes appeared in various combinations: often they were limited to one lung, sometimes to a single lobe, and occasionally they extended over several lobes in both lungs. The pleura, too, was frequently involved, with small unilateral effusions as a rule; however, on a few occasions fluid could be detected in both pleural cavities. A fairly common finding was thickening of an interlobar fissure suggestive of a small collection of fluid.

In addition to the group of patients under investigation the films of 25 children with acute glomerulonephritis whose chests had been x-rayed for various reasons during the 5 year period, 1949 to 1954, were available for reexamination. In some of them it was part of the routine investigation and in others it was carried out because of the presence of some clinical manifestations in the lungs or to assess the size of the heart. Among these 25 patients, 12 had radiologic changes in the lungs which closely resembled those observed in the first series. These must be regarded as a selected group and not as representative of the condition as seen in the cases between 1954 and 1957.

Thus, out of a total of 65 patients with acute nephritis, in all of whom the condition conformed to the accepted clinical pattern of the disease, 37 showed radiologically detectable lung lesions. The age incidence ranged from 1 year to 15, with the majority falling in the school age (Table I).

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Of the 65 children 63 recovered completely; 2 gradually passed into the chronic stage of nephritis with severe hypertension and ultimately died of heart failure.

Fig. 1 shows the distribution of the lung lesions, the right side being affected twice as often as the left (30 right, 15 left). On each side the lower lobe predominated, though on the right side upper and middle lobe involvement was as frequent as that of the lower. The incidence of pleural reaction was greater on the left but thickening of interlobar fissures was practically equal on the 2 sides.

The following cases have been selected as examples of the different types of lesions encountered.

Case 1. Brian C., a 5-year-old boy, attended the outpatient department because of cervical adenitis which had developed following a feverish illness, for which he had been treated with chloramphenicol for 2 days and for a further 2 days with a sulfonamide preparation. For the past few days he had been passing dark brown urine.

On clinical examination the child looked pale and tired. The left cervical gland was swollen (measuring about 1½:1 inch), slightly tender, and mobile. No abnormality was detected in the respiratory system. The liver edge was palpable 2 fingerbreadths below the costal margin and was firm and smooth. Liver function tests were normal; the tuberculin test was negative at 1:1000 dilution and the Paul-Bunnell test was negative. The white blood cell count was 11,100 per cubic millimeter, polymorphonuclear leukocytes 60 per cent, lymphocytes 38 per cent, monocytes 3 per cent, and eosinophils 1 per cent. The erythrocyte sedimentation rate was 30 mm. in the first hour, and the urine was smoky, acid, protein +, with a large number of red cells and a few granular casts in the deposit.

Table I. Age distribution and incidence of radiologic changes in the lungs of each age group

	No. of cases	*No. with roentgenographic abnormalities*
Under 3 years of age	3	2
3 to 6 years of age	19	12
6 to 10 years of age	29	15
10 to 15 years of age	14	8
Total	65	37

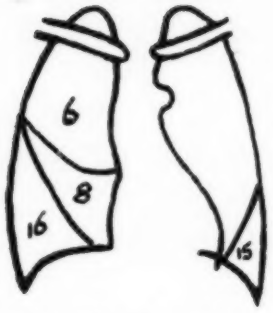

Fig. 1. Distribution of lung lesions.

Roentgenographically there was an opacity in the left middle zone, interpreted as partial collapse of the apical segment of the left lower lobe. There was also a small effusion at the left base (Fig. 2). Ten days later the pulmonary changes had practically cleared except for a slight pleural reaction at the left base (Fig. 3). The urine was completely clear, and the sedimentation rate was 12 mm. for the first hour.

Case 2. Stewart H. was 3 years old. Four days before admission the child became ill with vomiting and malaise which persisted for 24 hours. The urine appeared smoky 2 days later and the family doctor referred him to a hospital. A cough had been present for the past 3 days. No abnormality was found on clinical examination.

Laboratory investigations showed: White cell count 23,400 per cubic millimeter, lymphocytes 32 per cent, polymorphonuclear leukocytes 63 per cent, and monocytes 3 per cent. The erythrocyte sedimentation rate was 62 mm. in one hour, blood urea 30 mg. per cent, and the urine was acid, protein +, with a deposit of more than 50 red blood cells, approximately 10 leukocytes per high-power field, and a fair number of cellular and granular casts.

Roentgenogram showed some collapse of the right middle lobe and a degree of consolidation; the pleura was not involved (Fig. 4). Follow-up films taken a week later showed complete resolution. Within 14 days the nephritis had cleared.

Case 3. S. McD., a 6-year-old girl, had a "sore throat" about 3 weeks before her admission to hospital. The illness lasted 2 days and she was then perfectly well for a further 2 weeks. During the following week she became flushed, feverish, delirious, and subsequently lethargic. She had vomited on 3 occasions. Her appetite was poor, and a cough had become increasingly noticeable. Her mother had observed that the child's urine appeared reddish brown in color.

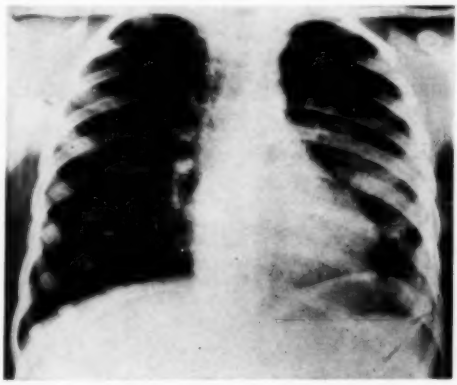

Fig. 2. Case 1. Opacity in the left mid-zone.

Fig. 3. Case 1. Roentgenogram taken 10 days after that shown in Fig. 2. Pulmonary changes have practically cleared except for a slight pleural reaction at the left base.

On examination the temperature was 98° F., pulse, 96; and respiratory rate, 26. There was slight edema of the eyelids and impairment of the percussion note at the base of the right lung; the breath sounds were unusually harsh and there were numerous medium räles audible over the same area. No other abnormal findings could be elicited. The blood pressure was 80/55 mm. Hg and blood urea, 230 mg. per cent. The erythrocyte sedimentation rate was 63 mm. for the first hour. The urine showed innumerable red cells, a few white cells, and granular casts. A roentgenogram of chest revealed partial collapse and possibly consolidation of the right lower lobe. A week later the lung x-ray showed considerable improvement and after a further week presented a normal picture (Figs. 5 and 6). The physical signs in the lung had cleared. At this stage the blood urea was 33 mg. per cent, but the erythrocyte sedimentation rate was 60 mm. for the first hour. The urine contained only traces of protein and a few red blood cells in the deposit. It was a further 4 weeks before the erythrocyte sedimentation rate reached normal values.

An entirely different aspect is illustrated by the following case:

Case 4. D. W., a 13-year-old boy, had an upper respiratory tract infection 1 week before the onset of symptoms; the mother then noticed that his legs were swollen and 2 days later the face was swollen. The urine was tested by the family doctor and contained protein +. During the night there were several convulsions. He was admitted to hospital in a stuporous state and shortly after arrival he had further convulsions.

On admission the blood pressure was 150/106 and there was edema of the face,

legs, and sacral region. The urine contained blood and protein; there were 18 red blood cells, and 16 leukocytes per high-power field, with a large number of granular and hyaline casts. The urine was sterile on culture. The blood urea was 70 mg. per cent. Throat swab revealed hemolytic streptococci, group A.

Within 12 hours he regained consciousness. The blood pressure increased to 160/110, and the blood urea to 90 mg. per cent. The urine output was 30 ounces per 24 hours. The erythrocyte sedimentation rate was 75 mm. in the first hour. Hemoglobin was 56 per cent.

Roentgenogram of chest taken on the day following admission, i.e., the sixth day after the onset of the nephritis, showed a generalized confluent mottling in the right lung field. In addition there was a degree of atelectasis of the left lower lobe and some soft mottling in the upper zone of the left lung (Fig. 7). There were no physical signs in the lungs. Within 3 days the lungs cleared almost completely (Fig. 8). Although there was only a trace of edema, there was only a slight loss of weight (2 pounds).

In the course of the following months the urine cleared completely, but the blood pressure remained somewhat raised, 135/80 mm. Hg, and the erythrocyte sedimentation rate was 30 mm. in the first hour. There was no edema and the urine output was normal. Within a further few days the patient relapsed, the urine again became blood stained, a throat swab showed the presence of hemolytic streptococci, group A, and the erythrocyte sedimentation rate again rose, but the blood pressure varied between 120/75 and 130/85. The blood urea did not exceed 50 mg. per cent.

His condition persisted unchanged for the next 2 months except for a slowly developing anemia. Following a blood transfusion the blood pressure was 195/115. Hypertension persisted and he died of cardiac failure 5 months after the onset of his illness.

Roentgenographic examination of the chest on 3 occasions before the terminal episode, but during the hypertensive phase, did not show any return of the original changes and the heart as well as the lungs seemed to be within the bounds of normal.

Fig. 4. Case 2. Partial collapse of right middle lobe and some degree of consolidation. Pleura was not involved.

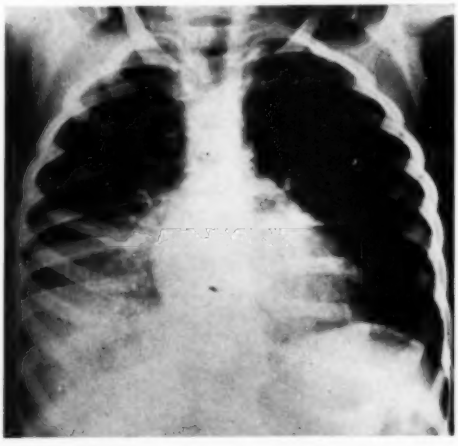

Fig. 5. Case 3. Partial collapse of right lower lobe and possible consolidation.

In view of the striking radiologic findings a careful search for clinical signs in the lungs was carried out in every patient with nephritis admitted during the period of the investigation (1954 to 1957). In the vast majority of cases this was largely negative and

Table II. Blood levels of urea in the cases of nephritis studied

Blood urea levels	*Roentgenographic lesions*	*No roentgenographic lesions*
25 to 40 mg. %	15	10
40 to 60 mg. %	8	12
60 to 100 mg. %	12	2
100 to 250 mg. %	2	4

Table III. Relationship of pulmonary changes to hypertension as assessed by diastolic blood pressure readings

Diastolic blood pressure (mm. Hg)	*Roentgenographic lesions*	*No roentgenographic lesions*
Under 70	15	8
70 to 89	7	13
90 and over	15	7

only in 1 case did the clinical examination suggest the extent of the lung lesion shown in the radiographs. In 7 of the 25 positive cases there were a few scattered rhonchi and coarse or medium râles over the areas involved. In the remainder, however, nothing could be found to indicate the presence of pulmonary pathologic changes even though they were sought with the prior knowledge of the roentgen appearances. The adventitious sounds gave the impression of bronchitis and cleared rapidly. Bronchitic signs were also elicited in 3 patients with radiologically normal lungs. The same paucity of clinical manifestations in the lungs became evident from the study of the case notes of the patients x-rayed during the years 1949 to 1954.

In the course of this study we gained the impression that the lung changes appeared in the first week after the onset of symptoms and underwent spontaneous resolution within 3 to 14 days after their detection. Their disappearance seemed to coincide with the onset of diuresis as judged by increased urine output and rapid weight loss, and in the later stages of the investigation we had already learned to predict the radiologic clearance of the lungs from the clinical phase of the nephritis.

An attempt was made to correlate certain manifestations of the disease with the radiologic findings. It was natural that we should examine the blood urea levels in these cases since the association of pulmonary edema with uremia had been described in adults in a number of publications over the past 25 years.[1-5] Table II shows blood levels of urea in the cases of nephritis studied.

Edema was marked in only 2 children; the majority of our patients with acute glomerulonephritis had only some puffiness of the eyelids although a small number also had swellings of the dorsum of the hands and feet. Of the 37 children with radiologic abnormalities in the lungs, 24 had clinically detectable edema while of 28 radiologically negative cases 15 had edema in the initial phase of the illness. Thus there was a slightly higher percentage (64 per cent) of children with clinically manifest edema among those who had lung changes in contrast to the incidence of manifest edema (54 per cent) among patients with normal radiographs of the lung. The difference, however, was not significant.

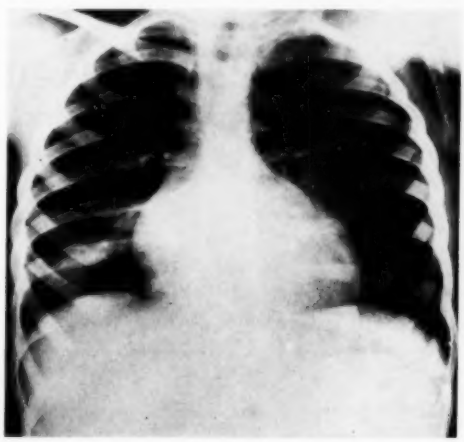

Fig. 6. Case 3. Roentgenogram taken 10 days after that shown in Fig. 5. Almost complete re-aeration.

Fig. 7. Case 4. Coarse mottling in the right lung field suggestive of pulmonary edema.

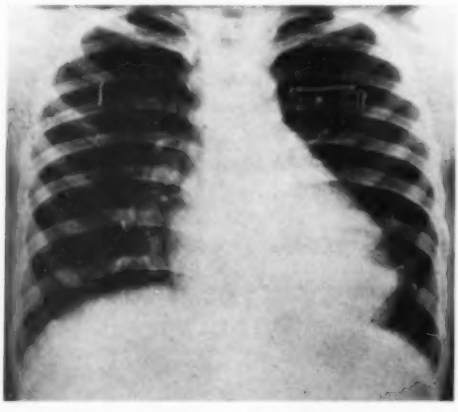

Fig. 8. Case 4. Roentgenogram taken 3 days after that in Fig. 7. Almost completely cleared.

The assessment of hypertension in young children is notoriously difficult. When blood pressure readings are persistently and excessively high, hypertension can be easily diagnosed. But if the increase is only of a minor degree it may only become evident in retrospect when normal levels have been attained again. Nonetheless, there seemed to be some correlation between hypertension and the discovery of pathologic findings. (Table III) shows this relationship. It is interesting to note that in half the number of children with hypertension the abnormal chest findings cleared several days before normal blood pressure readings were recorded.

DISCUSSION

The radiologic changes in 37 patients with acute glomerulonephritis fall broadly into 2 groups. In the first group there were only 2 cases. They showed a pattern already well known as the radiologic picture of pulmonary edema described in the adult as associated with uremia or with azotemic edema. In 1958 Nemir and Beranbaum[6] reported pulmonary edema occurring during the course of renal azotemia in a 10-year-old boy who had been suffering from renal disease from the age of 2½ years. The pulmonary edema was regarded as a result of cardiac failure since it cleared after digitalization; however, azotemia and vascular damage in the form of arteritis were thought to be contributory factors. In both our cases there was no definite evidence of cardiac failure and the pulmonary edema receded in a very short time without digitalization, although the hypertension still persisted. Diuresis, however, had started.

In the second group of 35 cases the lesions were partial collapse; consolidation, interlobar, and pleural effusions. The interlobar as well as the pleural accumulations of fluid were relatively small and they could only be demonstrated in patients examined during the first week of the illness. Recently it was possible to demonstrate in a child with glomerulonephritis not included in the main series that the pleural effusion was not of an inflammatory nature but that it was freely mobile in the pleural cavity (Figs. 9 and 10). We employed the method reported by Dunbar[7] at the IX International Paediatric Congress in Montreal (July, 1959) with which he achieved radiologic visualization of hidden pools of edema fluid in the pleural cavity in cases of nephrosis.

In the absence of histopathologic studies

of the lung tissues of patients showing the radiologic findings, any explanation of their nature and pathogenesis must remain conjectural. The 2 patients who succumbed to their illness and on whom detailed autopsies were performed died many months after their lung lesions had cleared. The possibility that some of the radiologic changes observed were of inflammatory origin, such as streptococcal pneumonia, cannot be ruled out. But consideration of the various facts revealed by this investigation allows the postulation of a hypothesis which may at least offer an explanation for part of the elicited findings. The presence of the lung lesions in the first week of the illness coincides with the development of hydremia[8] and hypertension. Their spontaneous and rapid resolution following the onset of diuresis and the free mobility of the pleural fluid suggest that they result from the accumulation of edema. It seems puzzling, however, that the typical picture of pulmonary edema was seen in only 2 out of 37 cases with pulmonary lesions.

The bronchial arteries supply the subpleural tissues of the pleural cavity, the interlobar space, the bronchial mucosa, and the interstitium of the lung parenchyma. If we assume that arterial constriction as a result of hypertension also affects the systemic

Fig. 9. Small pleural effusion left base.

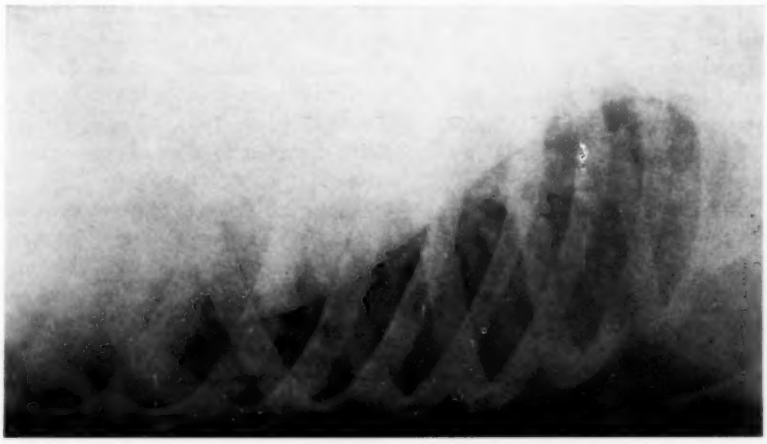

Fig. 10. Patient lying on his left side. Shows fluid to be freely mobile.

arteries of the lungs, this may then lead to a certain degree of ischemia with or without capillary injury. It is at least feasible that during the coincident phase of hydremia, edema develops in lung structures supplied by these vessels. This would explain the accumulation of fluid in the pleural cavities and in the interlobar space. The occurrence of lobular or even lobar collapse could be explained as a result of edema of the bronchial mucosa leading to occlusion of the finer ramifications of the bronchioles. The appearance of sharply localized areas of consolidation might well be accounted for by the development of edema in a limited part of the interstitial tissue with an associated effusion into the alveoli. Such consolidations might correspond with the focal edema or type III of the classification of pulmonary edema proposed by Gould and Torrance.[5] They describe it as a dense, homogeneous consolidation bounded by a major fissure or fissures predominantly lobar in distribution. It is interesting to note that they found only 3 cases of this focal type among a total of 100 patients with pulmonary edema and that all 3 were "complicated" uremias.

Only 2 of our patients developed hypertensive encephalopathy. In both of them it was the reason for their admission and blood pressure readings were 150/106 and 152/100 mm. Hg, respectively. Byrom[9] in his experimental study on the pathogenesis of acute hypertensive encephalopathy supports Volhard's view of local cerebral edema as a result of increased capillary permeability caused by arterial spasm. Both of these children also had pulmonary lesions and it is debatable if increased capillary permeability was also a contributory factor in these cases. Fishberg[10] in his book on *Hypertension and Nephritis* finds the concept of widespread capillary damage in glomerulonephritis attractive but unproved and disputed.

Fishberg[10] also mentions that diffuse bronchitis causing an annoying cough is not uncommon in acute glomerulonephritis. He regards pneumonia as a rare complication since the advent of the antibiotic era, although before this therapeutic advance it was by no means an unusual occurrence and he quotes Pospischil who found it in 11 per cent of his cases of postscarlatinal glomerulonephritis.

Peters[11] in a study of edema of acute nephritis in 97 adults postulated that the chief disorder responsible for it was congestive cardiac failure. A larger number of patients with edema fell into the group with the higher blood pressure, but there was not sufficient correlation between the two findings.

Radiologic examination of 32 patients with nephritis but without edema revealed 30 with no evidence of heart failure; 5, however, had pneumonia, 1 mild pulmonary fibrosis, and another fibrotic tuberculosis. The stage of the nephritis at which x-rays were taken was not mentioned. Among the 65 edematous patients, 28 had both cardiac enlargement and pulmonary congestion, 10 only cardiomegaly, 3 pulmonary congestion alone, and 2 pleural effusions. Dyspnea and even orthopnea seemed to be of common occurrence among his patients and was again accepted as a sign of failing cardiac function. Breathlessness was completely absent in the children in our series.

SUMMARY

During a 3 year period (1954 to 1957) all of the 40 cases of acute glomerulonephritis admitted to Booth Hall Hospital for Sick Children, Manchester, were submitted to x-ray examination of the chest. Twenty-five were found to have definite lung changes.

Among a further 25 patients of nephritis who had been x-rayed during the 5 year period 1949 to 1954, 12 had radiographic findings similar to those of the original group studied.

Segmental or lobar collapse, consolidation, intrapulmonary edema, and pleural effusions were the lesions encountered. They appeared in the first week of the illness and cleared with the onset of diuresis. The majority of these children had some degree of hypertension. There was no correlation with the age of the patients or the degree of azotemia present.

An explanatory hypothesis is discussed.

Our thanks are due to Dr. W. H. Patterson and Dr. M. L. Thomson, Consultant Paediatricians at Booth Hall Hospital for Sick Children, for permission to include their cases in this investigation. We would also like to express our thanks to Mrs. J. Walkden, Senior Radiographer, Booth Hall Hospital, and Miss J. Perry, Medical Illustrator, Crumpsall Hospital, Manchester, for their help with the x-ray studies and the illustrations.

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EDITOR'S NOTE

Some 20 years ago, Rubin and Rapoport (Cardiac Complications of Acute Hemorrhagic Nephritis, Am. J. Dis. Child. 55: 244, 1938) called attention to the relative frequency of cardiac involvement in acute glomerulonephritis which had not been generally appreciated prior to that time. The account published in this issue by Holzel and Fawcitt identifies a frequency not previously recognized of roentgenographically demonstrable pulmonary lesion in association with acute glomerulonephritis.

The pathogenesis of the lesions, if there is a single etiology, is unanswered. The hypothesis presented here, that the pulmonary changes are related to alterations in the extracellular fluid volume, is a possibility. However, in certain of the roentgenographic illustrations (see especially Fig. 2), the possibility of inflammatory changes, as indicated in the text, cannot be eliminated. Furthermore the assumption attributed to Dunbar,[7] that free movability of fluid within the pleural space is evidence of its noninflammatory nature, requires further substantiation. It would seem probable that in many instances such a conclusion would be the correct one. One should recall, however, that accumulations of pleural fluid in association with pneumococcal pneumonia at times do not proceed to empyema; this factor was observed even in the days prior to effective antimicrobial therapy. This pleural reaction is most likely inflammatory in origin and, prior to the development of a high fibrin content, the fluid is possibly movable with changes in position.

These considerations do not detract from the importance of the observations of Holzel and Fawcitt, but rather emphasize the need for further studies of the various manifestations of acute glomerulonephritis, their pathogeneses, and their significances.

W. E. N.

Diabetic and prediabetic pregnancies with special reference to the newborn

A 5-year study

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WITH THE STATISTICAL ASSISTANCE OF

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THE purpose of this paper is to analyze our experiences with infants born to 159 women, 97 of whom had clinical diabetes and 62 of whom had decreased tolerance to glucose. All 97 patients who were diabetic were receiving insulin.

The infants were delivered consecutively at The Mount Sinai Hospital† from November, 1952, through December, 1957, except for 19 who were delivered by the same group of obstetricians at other hospitals in New York City. Almost all of the newborn infants were observed and treated personally by the authors.

Fetuses of less than 28 weeks' gestation were considered as nonviable and those of 28 weeks or more as viable fetuses.

DIABETIC MOTHERS

Maternal management. Most diabetic patients were seen early in pregnancy, usually before the end of the third or fourth month. The last menstrual period and the expected date of confinement were estimated as accurately as possible. Clinic patients were examined every 2 weeks by both an internist and an obstetrician during the first 26 weeks of gestation and they were observed at least at weekly intervals thereafter. At the first visit a complete physical examination was carried out. A record was made of weight, blood pressure, hemoglobin concentration, blood group, serology, and Rh titer, and a chest roentgenogram and complete urinalysis were obtained. At each subsequent examination urine specimens obtained before meals

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†*Drs. Henry Dolger and John Bookman and their staff supervised throughout pregnancy the diabetic management of all the Maternity Clinic patients and of many of the private obstetric patients. The obstetric management of clinic patients was under the direction of Dr. Alan F. Guttmacher and his staff. Private patients were treated by various members of the attending obstetric staff. We are indebted to them for permission to include their private patients in our series.*

and at bedtime were examined for glucose and acetone. Determinations of blood urea nitrogen, total serum protein, serum albumin, and globulin concentration, serum cholesterol and cholesterol ester level, and blood glucose were made at the first visit and were repeated when indicated. The fundi oculi were examined at each visit. A diet of 1,500 to 2,000 calories with a moderate intake of carbohydrate, protein, and fat was suggested. Salt in addition to that used in cooking was prohibited. Patients who developed edema were restricted in their intake of sodium to 800 mg. a day. Vitamin supplements were prescribed. Hormones were not utilized. Mercurial diuretics or Diamox were ordered only in the presence of edema or beginning hydramnios. Patients were admitted to the hospital immediately if labor started prematurely or if there was evidence of hypertensive toxemia, acidosis, ketosis, sudden hydramnios or infection, or any other complication which might threaten the health of the mother or the life of the fetus. At about the thirty-third or thirty-fourth week of gestation, the internist and obstetrician conferred and selected the intended method of delivery. Most of the primiparae were scheduled for cesarean section between the thirty-fifth and thirty-seventh week. During the last year of the study, more primiparous patients were delivered vaginally, labor being induced by intravenous Pitocin drip. Multiparae who had had a previous cesarean section were delivered by this method again.

A few days before the date chosen for delivery a vaginal examination was performed and final choice was made between induction of labor and cesarean section. Cesarean section was performed if the presenting part was unengaged or if the cervix was long and closed. On the other hand, induction was attempted if the presenting part was engaged and the cervix was sufficiently obliterated to admit the examining finger. Induction was carried out by artificial rupture of the membranes alone, or by intravenous administration of Pitocin, followed by rupture of the membranes after labor was established. Vaginal delivery was conducted in the usual manner, analgesics being given in moderation. If attempts at induction were not followed by onset of labor in 12 to 24 hours or if the induced labor was not of the normally progressive variety cesarean section was done. In almost every instance cesarean section, either selectively performed or done intrapartum, was carried out under spinal anesthesia. The anesthetic used for vaginal delivery was either cyclopropane or a saddle-block type of spinal anesthesia.

Insulin was adjusted carefully during the days immediately preceding delivery. There was no consistent dosage pattern; some patients required more and some less insulin as the antepartal period progressed. On the day of delivery, insulin was omitted until after the birth of the infant.

Table I. Outcome of 177 pregnancies among 97 diabetic women: total life experience, present observation, and history compared*

	Present observation	*History*†
Total pregnancies (including 2 sets of twins)	126	53
Total pregnancy loss	29	36
Abortions‡	11	17
Stillbirths	10§	10
Live births	105	26
Survived 1 month or longer	97‖	17
Neonatal deaths	8	9
Per cent survived of:		
Total pregnancies	77	32
Viable pregnancies	84	47
Live births	92	65

*χ^2 *Significant:* P = less than 0.01 for all 3 sets of survival rates.

†Excludes pregnancies before diagnosis of diabetes. Also excludes 13 uncooperative patients because dates and outcome are not known.

‡Spontaneous abortions and miscarriages of less than 28 weeks' gestation.

§Includes one 600-gram, macerated, nonviable fetus; other twin survived.

‖Includes pair of *twins* and a surviving *twin*.

Outcome of pregnancy. The 97 diabetic women were pregnant 177 times. Our observations consisted of 124 pregnancies.* The

*Including 2 sets of twins.

records of 53 earlier pregnancies were carefully checked with previous hospital records elsewhere. The survival rates were much higher in the present series as can be seen in Table I. The differences were statistically significant. Since we are concerned primarily with the pediatrician's role as a member of the obstetrician-diabetician-pediatrician team, it should be noted that in our series there were only 8 deaths out of 105 live births, a survival rate of 92 per cent.

Seventy-one of 124 pregnancies were terminated by cesarean section and 53 infants were born vaginally. As seen in Table II, there was a higher incidence of stillbirths among the vaginal deliveries. This is, of course, due to the fact that infants who were known to have died in utero were delivered vaginally. Accordingly, the survival rate in Table II is meaningful only on the basis of live births. The difference between 3 neonatal deaths among the cesarean section group and 5 among the smaller vaginal group is statistically significant.

The rate of stillbirths reflects in part the difficulty of control in some patients. Among such were a drug addict, 2 patients with hypertension, 1 with a severe psychiatric problem, and 2 with recurrent ketosis.

Table II. Outcome of 124 pregnancies among 97 diabetic women by method of delivery*

	Cesarean section	*Vaginal delivery*
Total pregnancies (including 2 sets of twins)	73	53
Total pregnancy loss	4	25
Abortions†	–	11
Stillbirths	1‡	9
Live births	72	33
Survived 1 month or longer	69§	28
Neonatal deaths	3	5
Per cent survived of: *Live* births	96	85

*χ^2 *Significant*: P = 0.05.

†Spontaneous abortions and miscarriages of less than 28 weeks' gestation.

‡Includes one 600-gram, macerated, nonviable fetus; other twin survived.

§Includes pair of *twins* and a surviving *twin*.

Effect of duration of diabetes. There was no significant difference in rates of survival between the group with diabetes of less than 10 years' duration and that with diabetes of more than 10 years' duration.

A group of mothers with diabetes of 20 years' or more duration had an excellent record in 16 pregnancies. There were 2 spontaneous abortions and 1 stillbirth, with 13 of the 14 viable births, including a set of twins, surviving. There were no neonatal deaths in this group.

MOTHERS SUSPECTED OF BEING PREDIABETIC

Maternal management. Women who presented one or more of the following findings were selected for a dextrose tolerance test: (1) family history of diabetes, (2) history of symptoms of diabetes, (3) history of previous unexplained abortions and stillbirths, (4) history of previous delivery of one or more babies weighing more than 4,000 grams,[1] (5) positive test for glycosuria, and (6) fetus estimated at 3,100 grams or more on or before the thirty-sixth week of gestation.

Blood glucose levels following the ingestion of a 100-gram test meal were determined using the Somogyi-Nelson[2] method. Only those who had a decreased tolerance for dextrose according to the criteria of Wilkerson and Remein[3] on one or more occasions were included in this series.

There were 62 such patients. They were allowed to go to term and to deliver spontaneously unless it became apparent that the fetus was unusually large. If such were the case, pregnancy was terminated prematurely and delivery performed either vaginally by rupture of membranes and induction or by cesarean section.

Outcome of pregnancy. Table IV lists the outcome of 217 pregnancies (64 under our observation) among these 62 women.

Two of the 3 stillborn infants were large considering their prematurity; one fetus of 35 weeks' gestation and one of 38 weeks'

gestation, each weighed 3,800 grams. There were 3 neonatal deaths. Two of the mothers of these infants were hypertensive and obese. The third had had 3 previous stillbirths.

The spontaneous abortion rate and stillbirth rate in this group of 155 previous pregnancies were high, since unexplained previous spontaneous abortions and stillbirths were used as one of the criteria for performing a glucose tolerance test for the detection of prediabetic mothers. Some patients in this series were discovered to be potentially diabetic only after the fifth month of pregnancy. These factors explain the lower abortion figure in the group personally observed by the authors. There is no significant difference in the survival rate of live births between the group under present observation as compared with the "history" group.

PREDIABETIC MOTHERS

Nine of the 62 women who had abnormal glucose tolerance curves subsequently became diabetic while under our observation.

Table III. Outcome of 124 pregnancies among 97 diabetic women by duration of diabetes (personal observation)*

	Less than 10 years	*10 years and over*
Total pregnancies (including 2 sets of twins)	61	65
Total pregnancy loss	15	14
Abortions†	7	4
Stillbirths	3‡	7
Live births	51	54
Survived 1 month or longer	46	51§
Neonatal deaths	5	3
Per cent survived of:		
Total pregnancies	75	79
Viable pregnancies	85	84
Live births	90	94

*χ^2 *Not significant* for all 3 sets of survival rates.

†Spontaneous abortions and miscarriages of less than 28 weeks' gestation.

‡Includes one 600-gram, macerated, nonviable fetus; other twin survived.

§Includes pair of *twins*.

Table IV. Outcome of 217 pregnancies among 62 women with decreased glucose tolerance: total life experience, present observation, and history compared*

	Present observation	*History*†
Total pregnancies (including 2 sets of twins)	64	155
Total pregnancy loss	7	47
Abortions‡	1	25
Stillbirths	3	13
Live births	60	117
Survived 1 month or longer	57§	108§
Neonatal deaths	3	9
Per cent survived of:		
Live births	95	92

*χ^2 *Not significant*.

†Excludes 14 births of 1 patient because data were unreliable.

‡Spontaneous abortions and miscarriages of less than 28 weeks' gestation.

§Includes 1 pair of *twins*.

These 9, and another 17 in our series of 97 known diabetic patients, delivered infants before they actually had symptoms of diabetes. These 26 patients form a group in which the term "prediabetic" truly may be used, for they delivered infants both before and after they became clinically diabetic.

Outcome of pregnancy. These 26 women were pregnant 109 times, 76 before the development of clinical diabetes and 33 thereafter (Table V). The pregnancies were classified into 3 groups with reference to time of diagnosis of clinical diabetes. The survival rates for diabetic pregnancies were of the same order as for pregnancies occurring less than 5 years before the onset of maternal diabetes. In pregnancies occurring 5 years or more before the diagnosis of diabetes, the survival rates were significantly higher than in the 2 other groups. Our study indicates that the factors which are detrimental to the fetus of a diabetic mother are active in the 5-year period immediately before the onset of maternal diabetes but that they do not appear to operate earlier.[3]

OFFSPRING OF DIABETIC MOTHERS

Appearance. Numerous authors[4-11] have described the appearance of these infants and the problems that arise in their management. In our series, more than 60 per cent of the infants born to women with diabetes were visibly "puffy" in the neonatal period.

Our data indicate that respiratory difficulty was the most serious problem in the neonatal period. We found that all infant deaths due to respiratory causes occurred within 24 hours after delivery. If an infant with respiratory difficulty survived the first 24 hours, the outcome was favorable in every case.

Macrosomia. It is generally accepted that the body weight of infants of diabetic mothers is significantly greater than that of the offspring of nondiabetic women. Cardell[12] has collected data which confirm the generalized macrosomia, including the height, weight, and organ weight. He also compared the postmortem weights of the brains of infants of diabetic mothers with the brain weights observed in normal infants of similar body weight in a controlled series. Cardell noted that all the brain weights of the infants of diabetic mothers were below the average figures for normal infants of similar body weights in the control groups and also for those recorded by Potter and Adair.[13]

Table V. Outcome of 109 pregnancies among 26 prediabetic women in relation to time of diagnosis of diabetes

	Prediabetic state (years before diagnosis of diabetes)		
	5 or more	*Less than 5*	*Diabetic state*
Total pregnancies	36	40	33
Total pregnancy loss	6	13	9
Abortions*	5	4	3
Stillbirths	1	8	2
Live births	30	28	28
Survived 1 month or longer	30	27	24
Neonatal deaths	–	1	4
Per cent survived of:			
Total pregnancies	83	68	73
Viable pregnancies	97	75	80
Live births	100	96	86

*Includes septic, therapeutic, and spontaneous, abortions and miscarriages of less than 28 weeks' gestation.

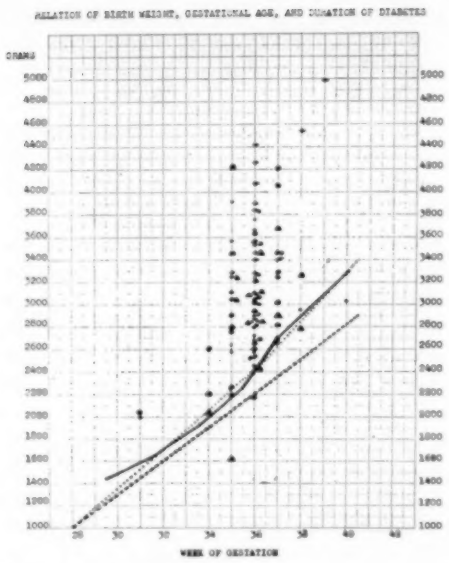

Fig. 1. o = less than 5 years,
+ = 5 to 9 years,
• = 10 to 14 years,
Δ = 15 years and over.
. . . . . , Scammon and Calkins.[14]
- - - - - - - , Streeter.[15]
————, Ellis and Lawley.[16]

The observed distribution of birth weights in our series of infants of diabetic mothers according to the gestational age and to the duration of maternal diabetes was compared with the normal mean values of Scammon and Calkins,[14] of Streeter,[15] and of Ellis and Lawley[16] (Table VI). Nearly all the birth weights in our series were distributed considerably above the normal mean values (Fig. 1). While this was true for the entire series, it appears that the infants of mothers, who were diabetic for 15 years or more had a lesser tendency to deviate from the mean of normal infants. Table VII shows the mean birth weight of infants born to mothers who had diabetes for 15 years or longer. No significant differences could be detected between the 5-year groupings of infants of

Table VI. Comparison of body measurements at birth of normal infants and infants of diabetic mothers (35 to 36 weeks' gestation)

	Infants of diabetic mothers (present study)			*Normal infants*[18]	
	Mean	*Standard deviation*	*Range*	*Mean*	*Standard deviation*
Head circumference	33.2 cm.	1.5 cm.	30.0 cm. to 37.0 cm.	31.6 cm.	1.5 cm.
Length	47.6 cm.	2.9 cm.	44.0 cm. to 53.5 cm.	—	—
Crown-rump	32.6 cm.*	2.0 cm.	29.5 cm. to 35.8 cm.	30.5 cm.	2.0 cm.
Birth weight	3,079 grams	485 grams	2,170 to 4,267 grams	2,272 grams	498 grams
Number of cases	45			41	

*Calculated for each infant from formula: CR = 0.66 total length + 0.5[20]

mothers with diabetes of less than 15 years' duration. Only one mother who had diabetes longer than 15 years had toxemia which might have caused a low birth weight.[17]

The increased length of infants of diabetic mothers is not as striking as is the increased weight. Table VI presents data comparing the head circumference, the total length (for infants of diabetic mothers only), the calculated crown-rump length,[14] and the birth weight of infants of diabetic mothers with similar measurements obtained in normal infants by Ellis and Lawley.[16] The comparisons are limited to infants with a gestational age of 35 to 36 weeks because there are too few infants in our series in the other gestational age groupings.

While the brain weight of infants of diabetic mothers may be low when correlated with total body weight, as noted by Cardell, our data on head circumference measurements appear to indicate a normal head size for the gestational age. Since total body weight may include an excess body water content, we believe it may be more accurate to correlate the size and weight of various organs with the gestational age or the crown-rump length as a basis for comparison.

Weight loss in neonatal period. The birth weights and also the per cent of maximum weight loss (where data were available) of infants of diabetic mothers have been compared with those of a group of infants of the same gestational age born to nondiabetic, normal mothers (Table VII). The differences are statistically significant, as measured by the variance of the means.* Delay in starting feedings in the infants of diabetic mothers undoubtedly contributes to the greater initial weight loss. Rudolph and coauthors[18] and Farquhar[11] have recently reported similar findings.

As previously noted, the offspring of women who had diabetes for more than 15 years weighed less than the infants whose mothers had diabetes of shorter duration. Despite lower birth weights, there was a somewhat greater initial weight loss in this group (12 per cent) than in the offspring of mothers with a shorter duration of diabetes, but this difference is not statistically significant.

Management of the newborn. One of us was present at or soon after delivery. Gentle aspiration of the nares and oropharynx was performed immediately, and oxygen was supplied by mask if there was any evidence of hypoxia. During the initial period of this study, the stomach was aspirated with a soft rubber catheter as originally suggested by Gellis and colleagues.[19] However, since 1956 this procedure has been discontinued; no change in the incidence of respiratory distress has followed. Small metal clamps (Hesseltine umbilical clamp) now in use have been very effective in preventing bleeding of the edematous umbilical cord.

*We have computed the variance of the means, in order to determine whether the differences between the several averages in Table VII are significant. The border line for significance of this test is the same level as for the χ^2 test described earlier, namely, the probability that the difference is due to chance at the 5 per cent level or in 1 out of 20 trials.

Table VII. Birth weight at a gestational age of 35 to 37 weeks and per cent initial weight loss of infants delivered alive* to diabetic women, women with abnormal glucose tolerance, and control women

	Birth weight (grams)				*Initial weight loss (per cent)*			
	Mean	*Standard deviation*	*Range*	*No. of cases*	*Mean*	*Standard deviation*	*Range*	*No. of cases*
All diabetic women	3,134	540	1,616 to 4,423	73	11.0	3.7	0.4 to 19.5	59
Diabetic less than 15 years	3,220	525	2,197 to 4,423	53	10.4	2.1	0.4 to 16.1	45
Diabetic 15 years or more	2,905	516	1,616 to 3,685	20	12.0	4.7	5.2 to 19.5	14
Women with abnormal glucose tolerance	3,198	522	2,210 to 4,080	19	7.7	2.7	3.5 to 11.9	18
Control women	2,853	545	1,620 to 4,030	78	7.0	3.7	0 to 20.5	78

*Excludes twins and infants whose congenital anomaly or illness would influence weight loss.

Table VIII. Neonatal deaths of infants of diabetic mothers

Patient	*Age of mother*	*Para**	*Duration of diabetes*	*Method of delivery*	*Gestational age and weight (weeks and grams)*	*Clinical manifestations*	*Age at death*	*Post mortem*
Baby O†	31	2-0-1-0	4	Vaginal	36 and 2,990	Abnormal pulmonary ventilation	18 hours	Brain congestion; hyaline membrane syndrome
Baby O†	32	3-0-2-0	5	Vaginal	36 and 3,510	Sudden death	8 hours	Intracranial hemorrhage, pulmonary congestion, anomaly of pulmonary valves (4 cusps)
Baby G	26	4-3-1-0	7	Vaginal	29 and 1,500	Abnormal pulmonary ventilation	2 hours	Not obtained
Baby A	27	0-0-0-0	10	Cesarean section	36 and 2,170	Abnormal pulmonary ventilation, cyanosis	20 hours	Not obtained
Baby M	26	0-0-0-0	18	Cesarean section	36 and 2,950	Cyanosis, dyspnea	12 hours	Congenital heart disease, transposition great vessels, Meckel's diverticulum, supernumerary thumb
Baby F	23	0-0-0-0	9	Cesarean section	40 and 2,268	Abnormal pulmonary ventilation	12 hours	Not done
Baby E	27	1-0-0-1	6	Vaginal	36 and 2,625	Intestinal obstruction	6 days	Malrotation of intestines, congenital ileal obstruction
Baby W	30	0-0-0-0	10	Vaginal	33 and 3,080	Abnormal pulmonary ventilation	18 hours	Atelectasis and hyaline membrane syndrome

*The parity formula used at The Mount Sinai Hospital denotes the following: number of full-term pregnancies, first digit; number of premature births second digit; number of early abortions, third digit; and number of living children fourth digit.

†Same mother gave birth to 2 dead infants.

Every infant of a diabetic mother was treated as a premature infant, regardless of the birth weight or gestational age. Each was placed in an "Isolette" type of incubator with full humidity and heat regulated to maintain relatively constant body temperature. Super-saturated mist was administered by nebulization either with compressed air or with oxygen providing an atmospheric concentration of 30 to 35 per cent. All infants delivered by cesarean section received 50,000 units of aqueous procaine penicillin twice daily for 3 days. If pulmonary infection was suspected or if abnormal pulmonary ventilation supervened, a wide-spectrum antibiotic was given. Vitamin K (Synkayvite), 1.25 mg., was injected after delivery and repeated in 24 hours.

Feedings were withheld for at least 24 hours after birth and often for 72 hours until respiratory distress had abated. Feeding by polyethylene gastric tube was used only for the most premature infants or for those too weak to suck. Parenteral fluids were rarely necessary. A formula of Alacta was offered for the first days of feeding. Later Lactum was substituted.

Digitalization was employed on occasions when heart sounds were of poor quality or when an enlarging liver or other evidences of cardiac insufficiency were present during the initial 48 hours. For initial digitalization, Lanoxin, a soluble solution of Digoxin, was used in a dose of 50 μg per kilogram of weight, half of the calculated dose being given immediately and one-fourth twice at 8-hour intervals. One-fifth of the initial digitalization dose was continued daily for 3 to 4 days. Electrocardiograms, which were obtained from 20 infants in this series, showed no consistent pattern of abnormality. We have not observed changes presumed to be due to hypokalemia, as reported by Bjorklund.[20] Although tremors were noted in many infants, glucose and calcium were rarely administered, as this symptom disappeared spontaneously. Hypoglycemia and tetany did not appear to be factors in the neonatal deaths in our series.

Neonatal deaths. Autopsy was performed on 5 of the 8 infants who died in the neonatal period (Table VIII). Three suffered from respiratory distress and 2 of these died with associated intracranial hemorrhage or congestion. "Hyaline membranes" were found in 2 infants who had respiratory distress. Three infants on whom permission for autopsy was not obtained also died in respiratory distress resembling that found in the 2 infants who had "hyaline membranes" at post mortem. All 6 infants who died of pulmonary causes lived less than 20 hours. Two succumbed as the result of congenital anomalies, one with complete transposition of the great vessels and the other with small bowel obstruction.

OFFSPRING OF MOTHERS SUSPECTED OF BEING PREDIABETIC

Physical characteristics. Sixteen out of 57 or 28 per cent of the infants who were born alive to mothers with histories suggesting prediabetes and with decreased glucose tolerance curves had the typical facies of the infant of a diabetic mother, i.e., edema and "jowls." This incidence was less than one-half that among infants of diabetic mothers. They also had fewer neonatal problems. We noted very few congenital anomalies in these infants, contrary to the report of Hoet and associates.[21]

Women with abnormal glucose tolerance gave birth to infants with high birth weights. The mean weight of their 19 infants was 3,198 grams, compared with 2,853 grams for the control infants. This difference is statistically significant. The neonatal weight loss was significantly less than that of infants of diabetic mothers, for contrary to the infants of diabetic mothers, these infants were fed earlier and began to nurse well on the second or third day of life. (Table VII).

It is assumed that some of the mothers who were included in this series may not be prediabetic since they were selected because of criteria which may,[22-25] but do not necessarily, mean that they will become diabetic.[3] The lower incidence of difficulty in the

perinatal period may be explained partially on this basis.

DISCUSSION

As noted by Miller[26] in a recent review of mortality statistics of pregnancies among diabetic women, it is extremely difficult to analyze results reported by various groups. There has been a lack of uniformity in the criteria employed for the classification of both maternal factors and for the stage at which fetal loss occurs. It is clear that even the best results reported indicate a significantly high rate of fetal loss among diabetic pregnancies. The pathogenesis of the detrimental factors operative upon the fetus are still unclear,[31] and there are questions concerning the management of the diabetic mother and her offspring[27] that remain unanswered despite the many reports in the literature.

It is certain that careful medical and obstetrical attention from the earliest weeks of pregnancy exert a favorable influence upon fetal survival.[31] Pedersen and Brandstrup[28] have shown that "long term" prenatal care (more than 53 days before the expected date of confinement) results in a more favorable outcome than does "short term" care. We wish to emphasize the importance of the pediatrician and the need for his presence at or soon after delivery.

The marked improvement in survival noted in our series when results of previous pregnancies are compared with those under a more organized approach can be ascribed largely to the management of the mother and her offspring as detailed above.

In his review of the literature, Miller[26] found a range of mortality in most recent reports varying between 18 and 27 per cent of viable births. In the present series, a mortality of 15.7 per cent of viable births compares favorably with these figures. A reported mortality of 10 per cent of viable births by Nelson and others[29] at the Boston Lying-in Hospital has thus far been the most favorable published. In their series of 163 cases, however, there were 35 spontaneous and therapeutic abortions, so that the total fetal loss was 29 per cent. In a later report of 802 patients, there was a fetal loss of 13 per cent after the twenty-eighth week of pregnancy.[30] Still another report,[31] in which "mist" was evaluated, stated that 15 of 100 *live born* infants in that series died, a much higher figure than those previously quoted from the same group. Pedowitz and Shlevin[32, 33] included prediabetic pregnancies in their series and reported a neonatal loss of 8 per cent. Farquhar's[11] figures almost parallel our data regarding neonatal deaths.

Unexplained death of the fetus late in pregnancy has influenced many obstetricians[34] to interrupt pregnancy between the thirty-fifth and thirty-seventh weeks. Others doubt the efficacy of this method of management since it substitutes the hazards of prematurity. Obviously some means are urgently required for determining which fetus is at risk if pregnancy is allowed to proceed and when it may be safe to do so. Given,[35] who has expressed considerable doubt as to the wisdom of routine intervention, nevertheless states that "when hydramnios develops, or progression of hypertension, or toxemia, I think the baby is sicker the longer it stays in the uterus, and that it has a better chance of living in the incubator." Our low neonatal mortality rate has encouraged us to continue our present policy of interruption of pregnancy at the thirty-fifth to thirty-seventh week or sooner if there is uncontrolled toxemia, since an excellently staffed nursery is available for the care of premature infants.

The duration of diabetes has been considered by some to influence fetal survival unfavorably.[36, 37] Of 14 viable infants in our series born to diabetic mothers of over 20 years' duration, only one was stillborn and there were no neonatal deaths. Another encouraging finding for the diabetic woman is our evidence, supporting that of Medovy,[38] that the occurrence of fetal or perinatal death does not rule out the probability of a normal infant being born in a subsequent pregnancy. Inasmuch as the noxious effect on the fetus precedes the clinical onset of diabetes by at least 5 years, a clearer under-

standing of this relationship will probably shed considerable light upon the endocrine interrelationships of the diabetic state.

Our management of the liveborn offspring of a diabetic mother has been outlined briefly. Until a great deal more is learned about the basic pathogenesis and physiologic aberrations of the condition, good medical and nursing care are probably the most important factors in saving fetuses.[27] Whether routine use of mist,[31, 39] glucose,[40, 41, 42] calcium,[43, 44] or digitalis therapy is of value is as yet unproved.

SUMMARY AND CONCLUSIONS

An analysis is presented of our experience with infants born to 97 diabetic women and to 62 women with histories suggesting the prediabetic state, corroborated by decreased tolerance to the ingestion of glucose. Methods of management of the mother and of the infant during the neonatal period are described.

Careful long-term medical and obstetric attention exert a favorable influence upon fetal survival. In the present series of 124 pregnancies among women with diabetes there was a total fetal loss of 23 per cent, a 16 per cent loss of viable births and a neonatal mortality of only 8 per cent. This is compared with the past-pregnancy experience of this group of women under other auspices; of 53 pregnancies there was a total loss of 68 per cent, a loss of 53 per cent of viable fetuses and 35 per cent of live births.

Factors detrimental to the fetus of a diabetic mother are active in the 5-year period immediately before the onset of maternal diabetes but do not appear to operate earlier. The outcome of pregnancies did not correlate with the duration of the diabetic state. In 16 pregnancies among mothers with diabetes of 20 years' or more duration, 13 of 14 viable births survived. Other evidence indicates that the occurrence of fetal or perinatal death does not rule out the probability of a surviving infant from a subsequent pregnancy.

The outcome of 217 pregnancies among 62 women with histories suggesting the prediabetic state and who had decreased tolerance to the ingestion of glucose has been tabulated. A fetal loss of 11 per cent of 64 pregnancies personally observed compares with a total loss of 30 per cent of 155 pregnancies by previous history. On the basis of the per cent of live births that survived, the two groups are essentially the same: 5 per cent died in the group observed and 8 per cent in the "history" group.

The management of infants born to diabetic mothers is reviewed. Careful observation and good medical and nursery care are considered the most important factors favorably influencing survival.

The authors acknowledge with thanks the work of Dr. Lotte Strauss who reviewed the material from necropsy and assisted in the tabulation of these data. We also acknowledge the critical suggestions of Dr. Ingve Larsson of Stockholm, Sweden.

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The use of exchange transfusion in salicylate intoxication

Report of 7 cases

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SINCE the advent of candy-flavored aspirin the prevalence of salicylate intoxication in children has increased. This form of toxicity constitutes 25 to 35 per cent of all types of poisoning in the pediatric age group.[1-3] Although the majority of these are mild, deaths do occur. In a recent survey during a 4 year period 380 deaths in children under 5 years of age were attributed to salicylism.[2]

The basic metabolic derangements consist of a respiratory alkalosis followed by a metabolic acidosis causing hyperpnea, lethargy, and coma.[4] Hypoprothrombinemia may result, leading to a bleeding tendency.

The usual treatment consists of gastric lavage followed by intravenous fluids and alkalinizing agents.[5] Vitamin K is used to prevent or correct the hypoprothrombinemia of this condition.

In the past decade exchange transfusion has been used for conditions other than hemolytic disease of the newborn.[6-9] Recently this procedure has been advocated as a method of treatment of poisoning. In 1955 Boggs[10] used this form of therapy for boric acid poisoning. He performed 2 exsanguination transfusions on a 12-day-old infant weighing 2.9 kilograms. At that time he suggested the use of exchange transfusion in other exogenous poisonings. Since that time there have been sporadic case reports in the pediatric literature concerning poisonings treated successfully with exchange transfusion. This method of treatment has been used in 4 cases of poisoning due to methyl salicylate,[11-14] 4 cases due to aspirin,[14-17] 2 cases due to ferrous sulfate,[18, 19] and single cases due to isoniazid,[20] pentobarbital, and pyridium.[15]

During the past 2 years, 7 cases of salicylate intoxication due to aspirin have been treated by exchange transfusion in our institution. This report summarizes our experience with this form of management.

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PRESENTATION OF CASES

Clinical findings. The initial major clinical and laboratory findings are summarized in Table I. The ages of our patients varied

Table I. Initial clinical and laboratory data

Subject	*Age (months)*	*Race*	*Sex*	*Weight (Kg.)*	*Amount of aspirin ingested (Gm.)*	*Time interval from ingestion to admission (hours)*	*Initial level of consciousness*	*Admission blood salicylate level (Mg. %)*
1	36	N	M	12.6	3.2 to 4.8	20	Coma	78.0
2	1	W	M	3.9	5.4 (in 3 days)	3 days (iatrogenic)	Listlessness	90.0
3	18	W	M	12.6	6.4 to 8.5	7	Irritability followed by coma	102.0
4	22	W	M	11.3	12.8	24	Coma	104.0
5	16	W	M	11.8	>5	5	Lethargy followed by coma	140.0
6	28	N	F	11.3	>8	3	Lethargy followed by coma	160.0
7	19	W	F	12.2	Unknown	6	Lethargy followed by coma	88.0

from 1 month to 3 years. In 6 the ingestion was accidental and in the seventh (1-month-old infant) the etiology was iatrogenic, occurring during a 3 day period. The amount ingested varied from 3.2 to 12.8 Gm. Coma was present on admission in 2 patients who had ingested the aspirin 20 and 24 hours, respectively, prior to admission. The others had only varying degrees of irritability and lethargy at the time of initial examination. Subsequently these latter individuals also developed a comatose state. Hyperpnea was present in each patient. At the time of admission Patients 4 and 7 were febrile, and Patient 4 had had a convulsion prior to admission. Patient 1 presented with congestive heart failure, which required digitalization shortly after admission. Gastric lavage was performed in Cases 3, 5, 6, and 7. Patients 1, 2, 3, and 4 received fluids with alkalinizing agents for periods from ½ to 14 hours prior to exchange transfusion. The remainder received exchange transfusions without previous intravenous fluid treatment.

Laboratory data. The blood salicylate levels at the time of admission ranged between 78 and 160 mg. per cent. In Cases 2 and 7 re-examination several hours later demonstrated a further rise. The carbon dioxide combining power of the blood was lowered in all instances. Hypoprothrombinemia was demonstrable in Case 1.

TREATMENT AND RESULTS

The exchange transfusions were performed by means of a cut-down procedure in the high saphenous vein with a polyethylene catheter. Local anesthesia was used for the incision.

The clinical and laboratory observations obtained during the exchange transfusions are presented in Table II. In 5 instances the volume of the exchanged blood equaled twice the estimated blood volume of the child. Three and four times the estimated blood volume was used in Cases 4 and 2, respectively. The duration of the procedure varied from 2½ to 4 hours. Calcium gluconate (10 per cent) was injected intravenously in 5 ml. amounts at a slow rate at the end of each 250 ml. of blood with the

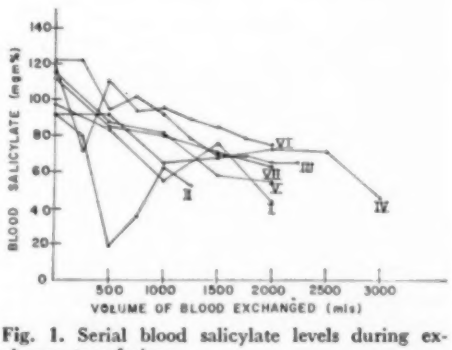

Fig. 1. Serial blood salicylate levels during exchange transfusions.

exception of Case 2 in which 2 ml. volumes were used for every 100 ml. of blood. Vitamin K_1 oxide was administered intravenously at the termination of the operation.

The most striking clinical observation during the exchange transfusion was the improvement in the state of consciousness and in the respiratory rate. With the exception of Patients 4 and 6, the patients showed improvement approximately midway through the procedure. In Case 4 convulsions and coma continued, and a deepening comatose state developed with the continuation of the transfusion in Case 6. At the conclusion, however, some improvement was noted.

The only unfavorable side effect occurred in Case 6. A shocklike condition was noted characterized by tachycardia and hypotension and followed by an urticarial rash. The clinical response was presumed to be an anaphylactoid reaction to the administered blood. Benadryl was injected intramuscularly and the unit of blood being administered was discarded. The exchange transfusion was then continued with a different unit of blood without any untoward effect. There was 1 death in this series. This patient (Case 4) continued to have convulsions and remained in coma, showing no evidence of improvement during the exchange transfusion. He died 10 hours later. Unfortunately, an autopsy was not obtained.

The immediate pre-exchange blood salicylate levels ranged between 90 and 121 mg. per cent. Levels taken at the end of the procedure were 43 to 75 mg. per cent. The average postexchange level was 53 per cent of the initial determination. Varying degrees of improvement were noted in the CO_2 combining power at the termination of the exchange transfusion in the 6 cases in which serial levels were obtained.

Serial blood salicylate levels were obtained during the transfusion at intervals of 250 to 500 ml. of infused blood in all cases (Fig. 1). In Cases 2, 3, 5, and 6 all of the blood was saved in 250 to 500 ml. portions. The total amount of salicylate contained in each of these volumes was determined. The total blood content of salicylate was determined from the blood salicylate level and the blood volume which was computed on the basis of 80 ml. per kilogram of body weight. The blood clearance was based on the drop in

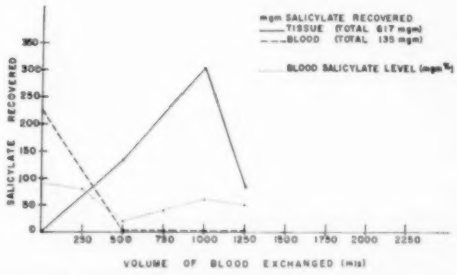

Fig. 2. Graph showing recovery of salicylate from blood and extravascular space, and serial blood salicylate levels in Case 2, during exchange transfusion.

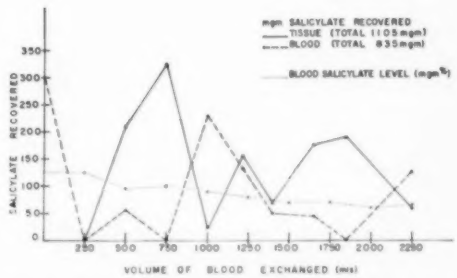

Fig. 3. Graph showing recovery of salicylate from blood and extravascular space and serial blood salicylate levels in Case 3, during exchange transfusion.

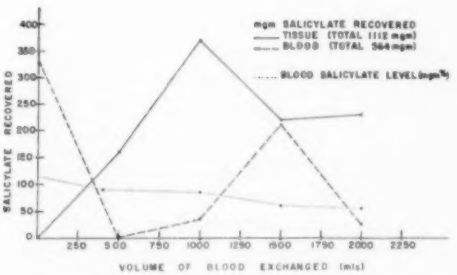

Fig. 4. Graph showing recovery of salicylate from blood and extravascular space, and serial blood salicylate levels in Case 5, during exchange transfusion.

Table II. Pre- and postexchange clinical and laboratory observations

Subject	*Weight (Kg.)*	*Time interval from admission to exchange transfusion (hours)*	*Amount of blood used (ml.)*	*Pre-exchange blood salicylate level (mg. %)*	*Postexchange blood salicylate level (mg.%)*	*Calculated blood clearance (mg.)*	*Total salicylate recovered from collected blood (mg.)*
1	12.6	6	2,000	97.0	43.0	---	---
2	3.9	14	1,200	90.0	51.5	135	752
3	12.6	3½	2,250	116.0	72.0	835	1,940
4	11.3	2½	3,000	92.0	46.0	---	---
5	11.8	4	2,000	115.0	55.0	564	1,676
6	11.3	2	1,900	121.0	75.0	517	1,826
7	12.2	7	2,000	112.0	61.5	---	---

the total blood salicylate content for any single period. The difference between the absolute amount of salicylate recovered in the collected portion and the calculated blood clearance for a particular interval represented the amount of salicylate derived from extravascular sources. In each instance in which this was done the amount of salicylate determined in the collected sample greatly exceeded the calculated blood clearance. These values varied with the size of the patient and volume of blood used. Figs. 2 to 5 represent the serial changes effected in the blood and tissue in the above 4 cases.

DISCUSSION

At the present time the use of the exchange transfusion in selected cases of poisoning appears to have a beneficial potential. This assumption is based on its availability in most centers and its easy application to infants and small children. The indications for its use have not been clearly established. Moreover, the transfusionist's technical competence and experience must be considered. The purpose of this paper is to report our experience in the management of salicylism in order to help establish such criteria. The majority of instances of salicylate intoxication are mild and easily managed by lavage and intravenous fluid and electrolyte therapy. A certain percentage of the severe cases cannot be cured by such treatment. It is in these situations that exchange transfusion appears to be beneficial. We have chosen the state of consciousness as the most important criterion for exchange. Usually this is associated with high levels of salicylate in the blood. In all of our cases this was greater than 90 mg. per cent at the time of decision for exchange transfusion. In late cases lower salicylate levels are associated with the comatose state and in these situations replacement transfusion also appears justified. In several instances unresponsiveness to trial periods of conservative management encouraged us in our decision to proceed with the transfusion.

Using from 2 to 4 volumes of blood we obtained a mean drop of 47 per cent of the initial blood salicylate level. Using comparable volumes in 1 case Heymann and associates[16] obtained similar results. Comparison with other reports is not possible because smaller volumes of blood were used.[14-17] Serial levels were taken during all 7 transfusions and were a guide to the effectiveness of the exchange. Clinical improvement in the

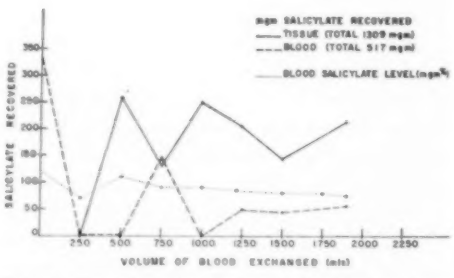

Fig. 5. Graph showing recovery of salicylate from blood and extravascular space, and serial blood salicylate levels in Case 6, during exchange transfusion.

Tissue/blood ratio of salicylate removed	Carbon dioxide combining power before transfusion (vol. %)	Carbon dioxide combining power after transfusion (vol. %)	Clinical observation during procedure	Subsequent course
---	9.0	27.0	Improved	Recovered
4.5/1	29.0	49.0	Improved	Recovered
1.3/1	21.0	33.0	Improved	Recovered
---	22.0	24.0	Not improved	Died (10 hours later)
2.0/1	16.0	25.0	Improved	Recovered
2.5/1	---	29.0	Allergic reaction	Recovered
---	24.0	32.0	Improved	Recovered

patient during the procedure was of considerable importance in determining the total volume of blood to be exchanged.

Although the serial blood salicylate levels give an indication of the change in the total body content of salicylate, the figures derived from the calculations in Cases 2, 3, 5, and 6 show that considerable amounts of salicylate are present in the extravascular space.

As is shown in Figs. 2 to 5, before a significant amount of salicylate can be recovered from the tissues a considerable amount must be removed from the blood. It can be seen that the exchange of at least a volume of blood equal to that of the patient is necessary to remove a significant amount of salicylate from the blood and a comparatively smaller amount from the extravascular space. In order to remove a significant amount of salicylate from the tissues at least an additional equal volume of blood is needed. When a relatively large amount of the salicylate is present in the tissues as in iatrogenic ingestion or relatively late severe cases it appears that larger volumes of blood are necessary for the removal of the drug from extravascular space (Fig. 2).

No serious side effects were noted except in one individual in whom an allergic reaction occurred. The blood being transfused was discarded; no reaction occurred with a different unit of blood.

The artificial kidney has been used[21-24] in the treatment of salicylate intoxication; however, it is not so readily available as the exchange procedure and requires a highly specialized team. Furthermore, it is not applicable to children under 2 years of age. Recently peritoneal dialysis has also been suggested as a form of therapy, but it has not yet been employed in humans.[25] To date the exchange transfusion appears to be the most rational and easily applicable method in pediatrics.

SUMMARY

The treatment of 7 patients with salicylate intoxication with exchange transfusion is reported. There were 6 recoveries and 1 death. This therapy appears to be valuable for severe salicylate intoxication in children. From the clinical and laboratory observations it is evident that at least twice the patient's estimated blood volume is necessary for effective exchange transfusion in such cases.

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Urinary tract calculi and nephrocalcinosis in infants and children

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THE consequences of nephrolithiasis or nephrocalcinosis in infancy and childhood are serious enough to encourage physicians to be aware of these problems. Early recognition may prevent the loss of functioning renal tissue, and the removal of complicating calculi usually improves the management of urinary tract infections. In some patients the presence of calculus serves as the initial complaint which leads to recognition of an underlying systemic metabolic disease such as hyperparathyroidism or renal tubular acidosis.

The physician's responsibility begins with the recognition of calculous disease but is not complete until he has utilized all available means to define, or encourage others to seek, the etiological factors involved. Unfortunately, once a calculus is discovered, emphasis is often placed only on the steps necessary for its removal and efforts to elicit disorders leading to calculous deposition are frequently neglected.

The purposes of the present report are to summarize the radiographic and clinical findings in 24 infants and children with calculous deposits in the kidney and urinary tract and, where possible, to emphasize the etiological factors related to such deposits.

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MATERIAL

Cases were selected from the Texas Children's Hospital and the Pediatric Division of the Jefferson Davis Hospital. Table I describes the patients studied, the circumstances under which the calcifications were found, and the associated clinical conditions. Since a number of the patients in this series were not studied in sufficient detail to determine the etiology of their condition, a definitive description of the causative mechanism is not possible for all cases.

RESULTS

Nephrolithiasis. The 15 patients with renal calculi ranged in age from 1½ to 14 years at the time of diagnosis. There were 6 male and 9 female children in the group. Fourteen were Anglo-American; 1 was Negro; none were Latin American. The socioeconomic status ranged from tenant farmer to upper middle class. Seven were considered to dwell in urban areas and 8 in rural areas.

All 15 of the patients studied (Patients 1 to 15 of Table I) had calculi which were

Table I. Clinical status of 24 patients with urinary tract calculi or nephrocalcinosis

Case	*Sex*	*Race**	*Age at diagnosis (yr.)*	*Initial complaint*	*Admitting impression*	*Duration signs and symptoms of stone*	*Method of diagnosis†*	*Location and roentgenographic appearance*	*Qual*
Nephrolithiasis									
1	F	W(A)	11	Frequency	Pyelonephritis	None	KUB	Right pelvis, smooth, homogeneous	--
2	M	W(A)	7	None	Hydronephrosis	None	KUB	Left pelvis, smooth, homogeneous	--
3	M	N	14	Hematuria, costovertebral angle pain	Nephrolithiasis	6 months	KUB	Both pelves, mulberry	Ca + OxPho
4	M	W(A)	3	Hematuria	Acute nephritis	2 days	KUB	Left pelvis, amorphous	CaOx
5	F	W(A)	13½	Costovertebral angle pain	Nephrolithiasis	6 months	KUB	Right pelvis, amorphous	--
6	F	W(A)	6½	Fever, general abdominal pain	Pyelonephritis	None	KUB	Both pelves, ureters, bladder; amorphous	CaMg PO_4
7	F	W(A)	4½	Fever, dysuria	Pyelonephritis	None	KUB	Right pelvis, staghorn	CaMg OxPho
8	F	W(A)	11	Hematuria, costovertebral angle pain	Nephrolithiasis	2 years	KUB	Both pelves, large, laminated	CaMg CO_3Ph
9	F	W(A)	6	Fever, dysuria	Pyelonephritis	None	KUB	Left pelvis, staghorn	CaMg OxPho
10	M	W(A)	1¼	Fever	Pyelonephritis	None	KUB	Left ureter, oval, amorphous	NH_4M Ox
11	M	W(A)	13	Gross hematuria	Nephrolithiasis	1 year	KUB	Right pelvis, mulberry	CaOx
12	M	W(A)	12	None	No disease	None	KUB	Right pelvis, smooth, homogeneous	MgCa OxPho
13	F	W(A)	13	None	No disease	None	KUB	Right pelvis, smooth, homogeneous	--
14	F	W(A)	9	None	No disease	None	KUB	Right pelvis, smooth, homogeneous	--
15	F	W(A)	7	Enuresis	No disease	None	KUB	Right pelvis, smooth, homogeneous	--
Vesical stones									
16	M	W(A)	⅓	Hematuria, dysuria	Nephrolithiasis	2 months	Stones in urine	Ureter and bladder, too small for description	CaOx Phos
17	M	W(A)	3½	Hematuria, dysuria	Bladder stone	1 year	KUB	Bladder, smooth, homogeneous	$CaNH_4$ OxPho
18	M	W(A)	2	Acute urinary retention	Acute bladder-neck edema	1 day	Cystoscopy	Bladder, not visualized	NH_4 PO_4
19	M	W(A)	5	Chills, fever	Chronic pyuria	None	Cystoscopy	Bladder, not visualized	CaOx Phos
20	M	W(A)	3½	Slow growth	Chronic renal insufficiency	None	Cystoscopy	Bladder, not visualized	CaMg Ox
21	M	W(A)	13½	None	Neurogenic bladder	None	KUB	Bladder, smooth, homogeneous	--
Nephrocalcinosis									
22	F	W(A)	1½	Anorexia, slow growth	Malnutrition, renal insufficiency	None	KUB	Diffuse, both kidneys; normal	--
23	M	W(A)	1½	Vomiting, headache	Renal insufficiency	None	Biopsy	Diffuse nephrocalcinosis; normal	--
24	F	W(A)	4½	Weakness, dehydration	Diabetes insipidus	2½ years	KUB	Diffuse nephrocalcinosis; normal	--

*A, Anglo-American.

†KUB, scout film of abdomen to include kidneys, ureters, and bladder.

‡Ca, calcium; Mg, magnesium; NH_4, ammonium; Ox, oxalate; Phos, phosphate.

Qualitative stone analysis‡	Urine					Serum				Etiology or associated condition	Recurrence
	pH	Specific gravity	Crystals	WBC	Ca	Ca	P	BUN	Cl		
--	5.0	1.022	No	Yes	No	10	4.4	21	104	Infection, ureteropelvic stenosis	No
--	5.5	1.030	No	Yes	--	--	--	--	--	Ureteropelvic obstruction, hydronephrosis	--
Ca + Mg OxPhos	5.5	1.023	No	Yes	Yes	15	2.6	20	97	Primary hyperparathyroidism	Yes
CaOx	4.5	1.016	CaOx	Yes	--	--	--	13	--	Ureteropelvic obstruction, hydronephrosis	No
--	6.0	1.020	No	Yes	--	--	--	15	--	Ureteropelvic stenosis, pyelonephritis	No
$CaMgNH_4PO_4$	6.5	--	No	Yes	--	9.1	5.1	13	--	Recurrent pyelonephritis	--
CaMg OxPhos	5.5	1.020	No	Yes	--	9.7	4.6	14	102	Recurrent pyelonephritis, bladder-neck stenosis	--
CaMg CO_3Phos	6.5	1.018	No	Yes	No	10.3	4.8	13	108	Recurrent pyelonephritis, ureteropelvic stenosis	No
CaMg OxPhos	5.0	1.023	No	Yes	No	9.2	5.7	10	102	Chronic pyelonephritis	Yes
NH_4Mg Ox	7.5	1.005	No	Yes	--	--	--	25	107	Bladder-neck stenosis, catheter, pyelonephritis	No
CaOx	5.0	1.023	No	No	--	--	--	16	--	Ureteropelvic stenosis, hydronephrosis	No
MgCa OxPhos	5.5	1.025	No	No	Yes	11.2	4.0	27	--	Immobilization, stasis, infection	Yes
--	5.5	1.012	No	Yes	Yes	10.6	4.8	22	105	Infection	--
--	5.0	1.016	No	Yes	Yes	12.0	6.1	8	104	Infection	Yes
--	--	--	--	--	--	--	--	--	--	None	--
CaOx Phos	6.0	--	No	No	No	10.2	5.0	10	104	None	No
$CaNH_4$ OxPhos	7.5	1.015	--	--	--	--	--	23	--	Indwelling catheter, infection, bladder exstrophy	--
NH_4PO_4	--	--	No	No	--	--	--	14	--	None	No
CaOx Phos	7.0	1.026	CaOx	Yes	--	--	--	--	--	Neurogenic bladder, infection, catheter	--
CaMg Ox	7.5	1.010	--	No	No	10	7	32	--	Bladder-neck stenosis, stasis	--
--	--	--	--	--	--	--	--	--	--	Neurogenic bladder, infection, catheter	--
--	7.0	1.008	No	Yes	Yes	14	6.2	50	--	Idiopathic hypercalcemia	--
--	4.5	1.019	No	No	Yes	16	6.1	46	100	Vitamin D intoxication	No
--	7.0	1.010	No	No	No	11	4.2	12	112	Renal tubular acidosis	--

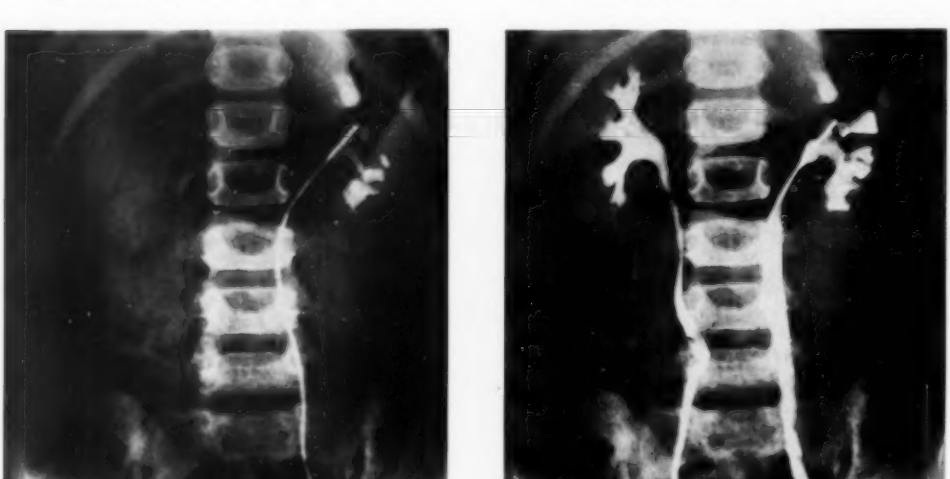
recognized first in the renal pelvis or upper urinary tract. In 6 patients the presence of calculus was suspected upon the basis of: hematuria in 2, hematuria plus costovertebral angle pain in 2 others, fever and generalized abdominal pain in 1, and acute costovertebral angle pain alone in 1. In the 9 other patients calculus disease was not clearly indicated by the patients' symptomatology (Fig. 1), although in all but 1 of these the prior history indicated the existence of circumstances likely to encourage calculus formation (e.g., chronic pyelonephritis, obstruction of the ureters, or immobilization and indwelling catheter drainage). In the 1 patient admitted for evaluation of enuresis, a small calculus was an incidental finding.

In the 6 patients with symptoms referable to nephrolithiasis, the duration of the findings prior to definitive diagnosis ranged from 2 days to 2 years.

The calculus formation was unilateral in 12 patients and bilateral in 3. One patient with bilateral formation also had a ureteral calculus. The presence of calculus was established by abdominal radiographic examination in all 15 patients by the presence of radiopaque calculi.

Qualitative analysis of the calculus following its removal or spontaneous passage was carried out in 9 instances. The stone was composed of a mixture of the salts of calcium and magnesium with phosphate and oxalate in 5 patients, of calcium magnesium ammonium phosphate in 1, and of ammonium and magnesium oxalate in another. Pure calcium oxalate stones were found in 2 other patients.

The radiographic features of the calculi



A *B*

Fig. 1. Case 9. Dysuria with fever brought this patient to the clinic where she was found to have pyuria but negative urine culture. Other studies failed to reveal additional etiological factors. The stone was removed and the pyuria was treated, but a small stone reappeared in the left pelvis 1 year later.

A, Staghorn calculus in left renal pelvis before pyelography.

B, After retrograde pyelography.

showed no close correlation with their chemical composition. The calculus appeared to be a smooth, homogenous concentration in 6 instances, while 4 other patients demonstrated amorphous ill-defined calculi. There were 2 patients with staghorn stones and 2 patients with mulberry stones. One patient had a large laminated stone.

Examination of random urine specimens revealed the presence of an acid urine pH (range 4.5 to 6.5) in all but 1 patient, although an alkaline pH was not unusual in random specimens. While concentration tests were not carried out in all patients, examination of random specimens revealed a range of urine specific gravity from 1.005 to 1.030. A specific gravity of 1.020 or above was found in 60 per cent of the patients studied. Crystalluria (calcium oxalate) was noted in only 1. Pyuria was present in all but 2, and in most it had been present continuously or intermittently for several years in spite of antimicrobial therapy. Calcium excretion in the urine was found to be excessive in 4 of the 7 patients in whom 24-hour calcium excretion was evaluated.

Blood biochemical studies were available in most patients. The value for serum calcium content was elevated in 3 and normal in 6. Serum inorganic phosphate values were normal in 8 and low in 1 (the patient with parathyroid adenoma). The blood-urea-nitrogen value was below 18 mg. per cent in 8 patients; it ranged from 18 to 27 mg. per cent in 5 others. Serum chloride values in 8 cases were not remarkable.

Associated with the nephrolithiasis were a series of complicating conditions. Seven patients had chronic or recurrent pyelonephritis of several years' duration. Six patients demonstrated definite roentgenographic evidence of stenosis at the ureteropelvic junction with hydronephrosis. Three patients had long-standing extensive muscular paralysis with stasis, immobilization, and osteoporosis (1½ to 5 years' duration). Two of these patients also had a chronic urinary tract infection. One patient had hyperparathyroidism (Fig. 2) due to parathyroid adenoma, and 1 had a bladder-neck obstruction with long standing hydronephrosis and pyelonephritis.

A

B

Fig. 2. Case 3. The patient was admitted with costovertebral angle pain and gross hematuria. Blood chemical findings were compatible with primary hyperparathyroidism and normal renal function. A parathyroid adenoma was removed; serum biochemical values returned to normal; later renal calculi were removed surgically.

A, Preoperative retrograde study shows opaque calculus at tip of right ureteral catheter.

B, Retrograde pyelogram confirms location in right renal pelvis.

Vesical calculi. Calculi were identified in the urinary bladder in 7 patients (No. 6 and 15 to 20). This group comprised 6 males and 1 female. They ranged in age from 4 months to 13½ years. In the 1 female (No. 6) the

calculi were thought to have originated in the renal pelvis, while in the 6 males the stones appeared to be primarily in the lower urinary tract. All patients were white and of Anglo-American extraction.

In 4 cases the bladder stone was not symptomatic; it was found incidentally in the course of roentgenographic survey of the abdomen in 2 and was identified at the time of cystoscopic examination in the other 2. Two patients were admitted because of gross hematuria and marked pain associated with micturition. A third (No. 17) had acute urinary retention and was thought to have a congenital bladder-neck stenosis complicated by infection; but cystoscopy revealed only the vesical calculus, the removal of which was followed by complete relief of the patient's symptoms.

The vesical stone was visible roentgenographically in only 2 instances, and in each the stone was smooth and homogeneous. One case was associated with exstrophy of the bladder and indwelling catheter drainage (Fig. 3); the other occurred in a child with a congenital neurogenic bladder. In a third case the calculi consisted of minute particles the size of sand and were too small to be visible radiographically. The calculi in the remaining 4 cases were radiolucent and not visualized.

Qualitative analysis of 6 of the vesical stones revealed 1 to be composed of calcium and magnesium salts with phosphate and oxalate. Two were composed of calcium oxalate and phosphate, 1 of calcium and magnesium oxalate, 1 of calcium and ammonium oxalate and phosphate, and 1 only of ammonium phosphate.

Laboratory studies in this group of patients were particularly deficient and contribute little to an etiological explanation.

Three patients had no associated structural defect of the bladder or urethra. Three others had chronic bladder-neck obstruction with residual urine and had had indwelling catheters for 1 to 3 years at the time a vesical stone was recognized; these 3 also gave a history of chronic, recurrent bladder infections. One patient had a chronic bladder-neck obstruction with residual urine but had not been treated with an indwelling catheter and gave no history of pyuria.

Nephrocalcinosis. Diffuse calcification of the renal parenchyma occurred in 3 patients. All were white Anglo-American children. Two were 18 months of age and 1 was 4½ years at the time of diagnosis. Two were female and 1 was male. In the male the possibility of nephrocalcinosis was suggested by the history of excessive vitamin D intake and the presence of hypercalcemia and hypercalciuria. Roentgenographic examination failed to reveal any unusual density in the kidneys, but biopsy of the kidney demonstrated amorphous calcium deposits in the peritubular connective tissue, particularly in the medullary regions. One female infant had a diffuse increase in the density of the kidney by roentgenographic examination suggesting nephrocalcinosis. She also had hypercalcemia and hypercalciuria plus the typical facies and changes in bone density characteristic of the severe form of idiopathic infantile hypercalcemia. This case has

Fig. 3. Case 17. This 3½-year-old male patient was found to have exstrophy of the bladder at birth; it was repaired surgically and continuous catheter drainage provided. In the interim there were many episodes of chills, fever, and pyuria in spite of vigorous antibiotic therapy. One year earlier he had had pain on micturition with terminal hematuria. A radiograph of the pelvis at that time showed the presence of a large, opaque bladder calculus.

Fig. 4. Case 24. This child had been ill since infancy with multiple episodes of weakness, pneumonia, vomiting, dehydration, polyuria, polydipsia, and severe anorexia. Growth and development had always been poor, and at 4 2/12 years her size was that of an average 2-year-old. Serum chemical studies revealed a persistent metabolic acidosis with hypokalemia and hyperchloremia in spite of which urine pH varied from 7.0 to 8.0. Radiograph of the abdomen showed multiple stippled areas of calcification in the renal parenchyma bilaterally.

been reported in greater detail elsewhere.[1] The third infant (Fig. 4) exhibited a chronically alkaline or neutral urine in the presence of systemic acidosis and hyperchloremia, characteristic of renal tubular acidosis.

DISCUSSION

Incidence. Although calculus disease of the urinary tract is one of the most common urinary problems encountered by the radiologist in the adult patient, the condition is uncommon in children. The possibility of calculus is frequently unsuspected until the condition is disclosed by radiologic examination. The low incidence of urinary calculi in the pediatric patient is exemplified by the scarcity of reported cases in the medical literature. This is particularly true regarding the pediatric and radiologic literature from the United States.[2] Most of the reports have appeared as single case presentations, although a substantial number of cases have been recorded in the evaluation of large series of calculi affecting all age groups. For example, Civilae,[3] reporting in the French literature, found in one series of 5,376 cases of urinary tract calculi that 45 per cent appeared in children. Thompson[4] reported from Chile that 25 per cent of the vesical calculi were in children. The incidence in this country is exemplified in Campbell's[5] series where only 0.42 per cent of 15,919 autopsies in children revealed calculus disease. Lattimer[6] states that in 1,252 urologic patients at Babies Hospital in New York City there were no examples of calculi. In our own institution between 1954 and 1959 in the course of 4,442 urologic radiologic procedures performed on approximately 3,800 children, 14 patients (0.37 per cent) were found to have urinary calculi. It has been suggested that variations in geographic incidence may be associated with poor nutrition consisting of low vitamin A intake and high alkaline ash residue.[6] The possibility of climatic factors and high incidence of dehydration with concentrated urine in warm climates has also been considered. Racial considerations are of interest in that there is a much higher incidence in the white race thin in Negroes. We have seen no example of calculus disease in a Latin-American child and only 1 in a Negro child (hyperparathyroidism), in spite of the fact that a significant proportion of the over-all patient material is Negro or Latin American.

There is reportedly no significant difference in sex incidence of calculus disease of the upper urinary tract, but bladder calculi are described more commonly in males than in females as a result of the higher incidence of bladder-neck obstruction in males. The shorter urethra in females may also enable them to pass small stones more readily.

The incidence of stones is more common in children below the age of 10 than after the first decade of life, possibly because of the fact that conditions serious enough to favor stone formation, such as anomalies

and infection, will have resulted in symptomatic complications during the first 10 years of life. Calculi have been reported in the fetus and in young infants.[7, 8, 9] The possibility that calculi in the young infant are more common than realized should be considered and may occasionally account for unexplained cases of colic and abdominal pain.

The average age at diagnosis in our series is 8 years; this conforms to the information gained from the literature that calculus disease in children is more common during the first decade. The sex incidence was not significantly different regarding upper urinary tract calculi, but all of our patients with bladder calculi were males.

Etiological circumstances. The cause of nephrolithiasis is unknown; in spite of many studies the significance of such factors as stasis, hypercalcemia, diet, and infection in the origin of calculi remains obscure. The controversy in this area has been well summarized by McGeown,[10] who feels that three theories deserve further consideration: (a) deficiency in the urine of some substance which prevents calcium precipitation (e.g., citrate, urea, magnesium, hyaluronic acid, galacturonic acid, glucuronic acid, ascorbic acid, gluconic acid, or amino acids); (b) an increase in a calcium precipitating agent (e.g., a mucopolysaccharide which has been shown to be a principal constituent of the matrix of stones); and (c) minute deposits of calcium in renal lymphatics (microliths) which are later extruded into urine.

Table II. Circumstances associated with stone formation in 15 patients with nephrolithiasis and 7* patients with vesical calculi

Finding	*Nephrolithiasis*	*Vesical calculi*
Obstruction plus infection	5	3
Obstruction alone	3	1
Infection alone	2	1
Immobilization plus infection	3	0
Hyperparathyroidism	1	0
None	1	2

*One patient had both upper urinary tract and vesical calculi.

Table III. Chemical findings

Determination	*Number*	*Normal*	*Abnormal*
Serum calcium			
Nephrolithiasis	9	6	3
Vesical calculi	3	3	0
Nephrocalcinosis	3	1	2
Urinary calcium			
Nephrolithiasis	7	3	4
Vesical calculi	2	2	0
Nephrocalcinosis	3	1	2

The relationship of stasis, infection, and hypercalciuria is a perplexing one. While urinary tract calculi are frequently associated with infection and urinary stasis (Fig. 5), many patients with chronic genitourinary infection and/or stasis escape calculus disease (Table II). Similarly, not all patients with hypercalciuria have stones; and not all patients with stones are found to excrete an excess of calcium in the urine (Table III). It would appear then that the latter factors may be more important in the growth of calculi than in their origin.

Altered metabolic processes may account for urinary tract calculi but more commonly produce nephrocalcinosis or calcification within the renal parenchyma. Conditions which may account for disturbances in calcium metabolism and resulting nephrocalcinosis are hyperparathyroidism, Cushing's disease, administration of cortisone, idiopathic hypercalciuria, immobilization hypercalciuria, idiopathic hypercalcemia, and renal tubular acidosis. Cystine calculi occur in a minority of individuals who have excessive urinary excretion of cystine on a hereditary basis.[11] By contrast, calculi do not occur in cystine storage disease with aminoaciduria (Fanconi syndrome).

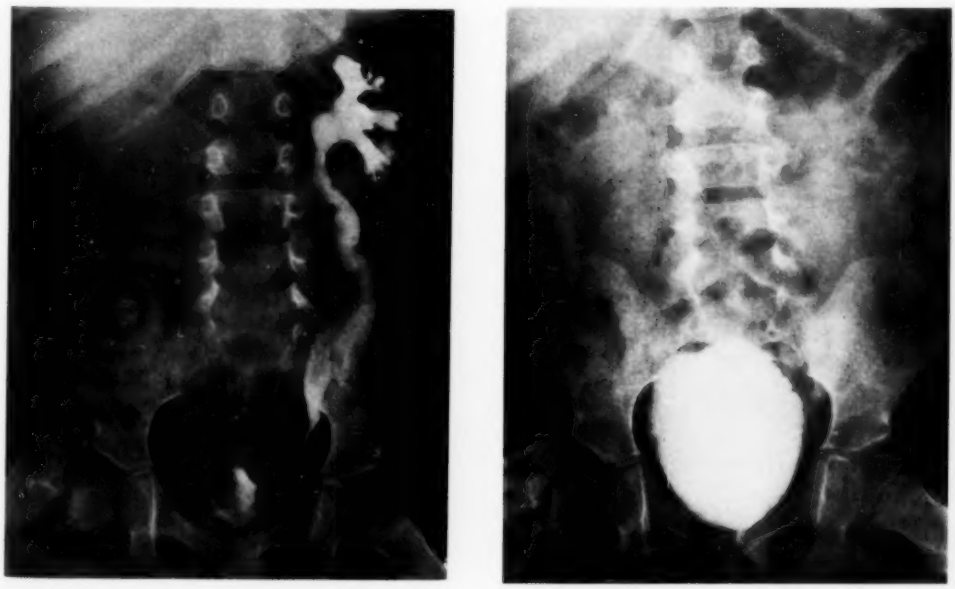
Higgins[12] has suggested that vitamin A deficiency leads to hyperkeratinization of urinary tract epithelium with increased formation of potential stone nuclei. Unfor-

tunately, clinical evidence has not given support to this interesting experimental observation.

Bladder calculi are usually associated with bladder outlet obstruction, foreign bodies, neurogenic dysfunction of the bladder, or long-standing catheter drainage.

Chemical composition. For proper therapy and prevention of recurrences every stone should undergo chemical analysis. This is important for the chemical composition may provide significant information as to its etiology.[13] Rusche and Morrow[14] state that 30 to 50 per cent of calculi in children are composed of urates or uric acid; and Campbell[5] describes the incidence of various types of stones in children in decreasing order of frequency as: uric acid, urates (ammonium, potassium, and sodium), oxalates (calcium, magnesium, and ammonium), phosphates (calcium, ammonium, and magnesium), carbonates (calcium, ammonium, and magnesium), and cystine and xanthene.

The absence of uric acid stones in the present material is unexplained. Although the uric acid per se is not radiopaque, the presence of calcium salts incorporated within their substance occasionally makes them visible by radiographic means. In the course of some 700 autopsy examinations in this hospital no uric acid stones have been noted[15]; and Nicholas and Leifeste,[16] reporting from this area on the chemical composition of 1,700 stones from all age groups, found only 2.6 per cent composed of uric acid. Magnesium-ammonium-phosphate stones are more often associated with extensive chronic urinary tract infection, obstruc-



A *B*

Fig. 5. Case 18. This child was found at birth to have hydrocephalus, spina bifida, and a neurogenic bladder. Catheter drainage was instituted and there were intermittent pyuria and febrile episodes for 5 years at which time a large bladder stone was recognized and removed surgically.

A, Left retrograde pyelogram showed stricture of the inferior portion of the left ureter with associated hydroureter and mild calycectasis. A radiolucent calculus was identified in the bladder (arrow). Note old fracture deformity of right hip and extensive spina bifida.

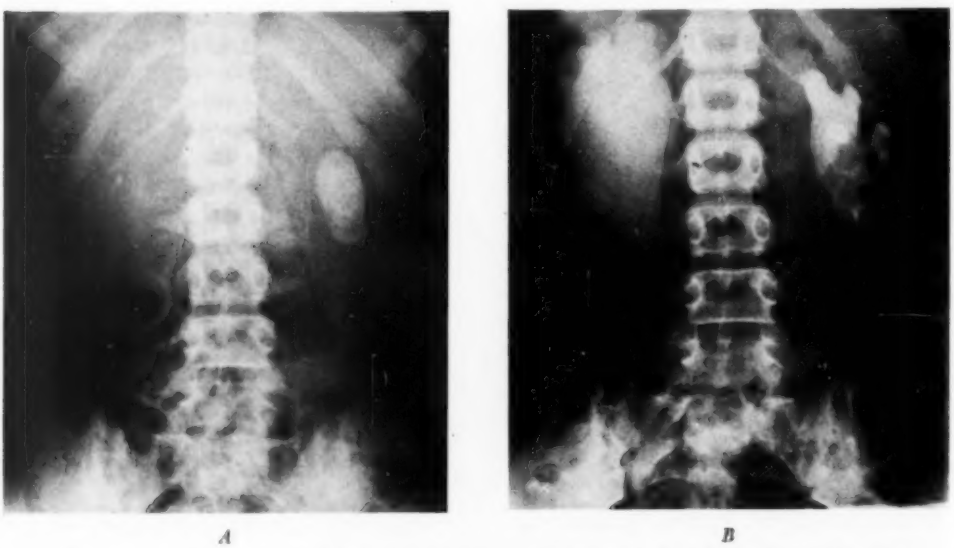
B, Cystogram showed increased trabeculation and cellule formation of the bladder as well as vesicoureteral reflux on the left.

tion, and an alkaline urine. These stones are soft, often amorphous; they may fill a calyx or the entire renal pelvis or may lie in the bladder. Calcium-containing stones (e.g., calcium oxalate, calcium phosphate, or calcium carbonate) usually form in alkaline or neutral urine in association with some condition leading to hypercalciuria and are quite radiopaque. The oxalate stones are usually hard and dark in color with a spiculated or mulberry contour. Calcium-phosphate stones are usually small, laminated, light colored, and also radiopaque. Calcium-carbonate stones are soft and brittle and have a consistency similar to that of chalk. Any of these calcium-containing stones may develop in patients with hypercalciuria (e.g., hyperparathyroidism, oxalosis, excessive intake of calcium, and/or of vitamin D, renal tubular acidosis, chronic pyelonephritis, inability of the renal tubules to form ammonia, or prolonged immobilization).

Chemical analysis of the calculus was made in 14 of the cases recorded here. In all cases, with the exception of one, the analysis showed a mixture of many calcium compounds—usually calcium oxalate, calcium phosphate, and calcium carbonate. Even in those cases in which there was no radiographic visualization of calculi, calcium salts were often present. Presumably in such cases the stones were of such a small size as not to be identifiable on radiographs. There were no examples of uric acid stones or urates; this negative finding contrasts markedly with Campbell's estimation that most urinary calculi are composed of uric acid.

In the 22 infants and children with stones the overwhelming majority were associated with a combination of infection and congenital obstruction. The apparent etiological circumstances in these cases are listed in Table II.

Of the types of congenital obstruction, 6 were bladder-neck obstructions or obstructions in the proximal urethra, 4 were strictures at the ureteropelvic junction, and 1 was a case of exstrophy of the bladder which



A *B*

Fig. 6. Case 13. This 13-year-old child had recurrent episodes of chills, fever, hematuria, and flank pain for 3 years associated with pyuria.

A, Roentgenograms at 13 years of age revealed bilateral stones.

B, Retrograde pyelography demonstrated marked hydronephrosis on the right and chronic pyelonephritis on the left with bilateral ureteropelvic obstruction.

had been treated by prolonged catheter drainage. A chronic infection without obstruction was found in only 2 cases. Three of the cases were examples of nephrocalcinosis and were not associated with free calculi within the collecting structures of the kidneys. There were no examples of what could be considered primary calculi, in other words, calculi developing independently of either obstruction or infection.

Radiographic findings. Definite radiographic evidence of opaque calculi was shown in 15 cases; the degree of opacity is shown in Table I. One of these cases showed amorphous density occupying the inferior calyx of the left kidney, but it was not until the right renal structure was filled with contrast material that amorphous radiolucent material was identified in the right renal pelvis. Typical mulberry stones, composed primarily of calcium oxalate, were identified in 2 cases. The largest calculus, measuring 6 cm. in length and occupying the entire left renal pelvis, was found in Case 8 (Fig. 6). This calculus was distinctly laminated and composed primarily of calcium phosphate and calcium carbonate. Two of the cases (Nos. 7 and 9) showed characteristic staghorn calculi. Although 7 bladder calculi are included, only 2 were visualized (Nos. 17 and 21). One ureteral calculus was identified in Case 6. One case of nephrocalcinosis could not be appreciated by film evidence but was identified by renal biopsy (No. 23). The other case showed increased density of the entire kidney, but without calculi.

Symptomatology. Sixty per cent of urinary calculi in children are silent.[12] When symptoms are present they may consist of abdominal pain, backache, nausea and vomiting, diarrhea, anorexia, fever, and convulsions. Pyuria is the most common clinical sign and occasionally hematuria may be present.

Bladder calculi often produce extreme discomfort on standing, a discomfort which is relieved when the child lies supine. An additional characteristic of bladder calculi is sudden excrutiating pain on voiding. Bladder calculi are occasionally associated with hemorrhoids or rectal prolapse due to straining on micturition, and in boys abnormally frequent priapism may be present as the result of reflux neurogenic mechanism initiated by irritation of the trigone and the bladder neck. A rare complication of extrusion of the stone through the bladder wall into the paravesical space has been reported by Campbell.[5]

Since nephrocalcinosis is usually secondary to an underlying disturbance in calcium and phosphorus metabolism, signs and symptoms are those of the primary disease. Idiopathic hypercalcemia is characterized by failure to thrive, irritability, and the finding of hypercalcemia. Renal tubular acidosis should be suspected in the presence of episodes of dehydration with acidosis in which an alkaline or neutral urine pH is found in the presence of reduced plasma bicarbonate and elevated plasma chloride levels. Vitamin D intoxication is characterized by the signs and symptoms of hypercalcemia and hypercalciuria due to any cause, such as polyuria, polydipsia, headache, anorexia, hypertension, hematuria, or renal insufficiency.

SUMMARY

1. Clinical experience with a group of 24 patients showing urinary tract calcium deposits is described. Fifteen had stones in the upper urinary tract, 6 had bladder calculi, and 3 had nephrocalcinosis.

2. Although the etiological basis for the origin of calculi is unknown, the presence of stasis and infection appear to be significant factors in the development of calculi of clinically significant size.

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Systemic deposition of metallic mercury

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Two cases of systemic deposition of metallic mercury are presented and previous reports are briefly reviewed. Routes of entry, travel, and deposit of this metal are discussed.

CASE REPORTS

Case 1. A 4-year-old Negro boy was seen at The Johns Hopkins Hospital with a chief complaint of "falling, unconsciousness, and jerking of the extremities" of 1 day's duration. Except for 5 days of oxygen therapy during the neonatal period, the past history was unrevealing. Careful inquiry elicited no information which would suggest the entrance of metallic mercury into the body. Physical examination was unremarkable. Laboratory studies, which included lumbar puncture, blood calcium, phosphorus, urea nitrogen, and fasting glucose determinations, were within normal limits. Mercury excretion during a 24-hour period, as determined by the polarographic method, was not significant.

X-ray examination of the skull, neck, and trunk (Figs. 1, 2, 3) revealed the presence of many small round shadows of metallic density no larger than 1 mm. in diameter. Some of the intracranial densities were surrounded by a sphere of less marked density. In the neck the distribution of the dense shadows showed preferential concentration in the thyroid gland. Deposits were also present in the heart, the lungs, the liver, and the soft tissues. Biopsy of the thyroid isthmus showed the presence of small deposits of material which was indistinguishable from metallic mercury. The deposits were surrounded by foreign-body reaction.

Case 2. An 11-year-old white girl was seen at the Clinical Center of the National Institutes of Health for evaluation of heart disease, presumably of congenital or rheumatic origin. After complete cardiac evaluation, the final diagnosis was rheumatic heart disease without evidence of a shunt.

Chest x-rays showed small, round metallic densities in both lungs which were most concentrated in the superior segment of the left lower lobe and the apical posterior segment of the left upper lobe (Fig. 4). Review of the referral records indicated that the presence of "peculiar shadows in the lungs" was noted following right cardiac catheterization whereas no such lesions were present prior to the procedure. This was interpreted to indicate that during anaerobic blood sampling some mercury inadvertently had leaked into the catheter and right side of the heart. No unusual reaction to the catheterization was recorded.

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A

B

Fig. 1, *A* and *B*. Multiple round metallic densities, scattered intracranially as well as throughout the soft tissues of the neck, are shown. There is particular concentration in the thyroid region.

DISCUSSION

Several reports have been written concerning the introduction of metallic mercury into the body by various routes.[2, 3, 6, 7] The metal will not cause symptoms in the intact gastrointestinal tract. In fact, mercury has been used in quantity in attempts to relieve obstruction. Formation of intraperitoneal mercury granuloma has been reported in a case of perforated appendix due to rupture of a mercury-weighted Honors-Smathers tube which was placed in the jejunum.[3] The mercury globules remained fixed in the periappendicial granulomatous mass.

The aspiration of mercury following ingestion and subsequent regurgitation by a patient who attempted suicide resulted in deposition of small globules in the lungs.[7] After subsidence of acute pneumonitis, the patient became asymptomatic and no change was noted in the chest x-ray over the following 5 years.

During anaerobic blood sampling, mercury may accidentally be introduced into the punctured vessel.[9] In 2 cases of peripheral mercury embolism occurring during sampling from the brachial artery, acute pain, swelling, and redness of the hand gradually subsided after 2 weeks. In 1 patient, mercury globules sloughed from finger-tip granulomas for 1 year and occasionally thereafter. Neither patient showed signs of systemic mercury poisoning. X-rays showed scattered metallic nodules of less than 1 mm. in diameter in the peripheral soft tissues of the fingers.

In a patient who deliberately injected 2 c.c. of mercury into his own vein, questionable transient signs of mercury toxicity (anorexia, abdominal pain, diarrhea, loss of weight, gingivitis, and microscopic hematuria) were noted.[2, 8] Chest x-rays showed intracardiac and pulmonary deposits of mercury, which were very similar in appearance to our 2 cases (Figs. 3 and 4). The patient succumbed to tuberculosis 7 years later.[7] At autopsy metallic mercury globules were present in the heart, lungs, kidney, liver, and spleen.

In still another case in which it was al-

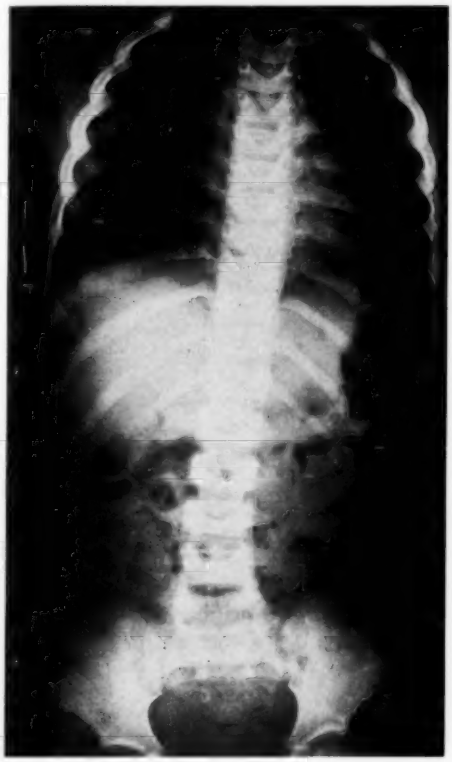

Fig. 2. Similar deposits are seen in the heart, lungs, liver, and skeletal muscle.

leged that mercury had been introduced intravenously by self-injection with partial extravasation into the antecubital fossa, sloughing mercury granulomata developed in this region and in the knee and thigh region of the contralateral leg where no mercury had been introduced.[1, 4] Ten months after the injection deposits of mercury were demonstrated in the lungs and heart by chest x-ray. Two years later the patient died of miliary tuberculosis. Autopsy showed mercury in the lungs, heart, and spleen.

No systemic ill effects have been reported following experimental subcutaneous injection of metallic mercury up to 6 Gm. in tuberculous and syphilitic patients.[6]

In experiments in rabbits intravenous injection of metallic mercury up to 1 per cent of body weight was tolerated without immediate deleterious effects.[6] In sacrificed animals the mercury has been shown to travel through the pulmonary capillaries, unite into larger globules, and be deposited in the pulmonary veins, alveolar septa, and regional lymph nodes.[2]

In our first case the history does not reveal the portal of entry. The distribution indicates a hematogenous route of deposit.

A

B

Fig. 3, *A* and *B*. Films of the neck demonstrate numerous deposits in the thyroid gland.

A

B

Fig. 4, *A* and *B*. Scattered small metallic densities are seen in the lungs. They were noted subsequent to cardiac catheterization.

Intravenous introduction with passage through a patent foramen ovale and/or through the pulmonary circuit and peripheral arterial distribution, predominantly to the head and neck, resulting in multiple emboli, would explain the present findings.

There are few differential considerations for small globular deposits of metallic densities with or without surrounding less dense zones of reaction. Bullet fragments or lead shot rarely have to be considered because of their distribution and shape. Other heavy-metal and metal-salt deposits such as bismuth in the gluteal areas and materials of diagnostic contrast which have extravasated into various regions are usually readily differentiated.

Cysticercosis has been described to show radiologically small round calcific densities with surrounding less dense zones, the central area representing calcified scolices and the outer one the surrounding cysts.[10] The route of larval deposit is the blood stream and the favored sites of cysticerci are muscle and brain. History and laboratory work up might not be helpful. Biopsy will often be resorted to for diagnosis.

CONCLUSIONS

1. History of accidental or intentional mercury injection may not be readily elicited. Negative history and physical examination does not exclude metallic mercury deposition from differential consideration of positive x-rays.

2. Chronic systemic toxicity has not been reported in cases of metallic mercury deposits. Foreign-body granuloma formation occurs at sites of interstitial deposits and emboli. This process would explain well the symptoms in our first case.

3. Anaerobic blood sampling with mercury in the syringe is accompanied by risk of accidental injection of metal.

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A case of measles encephalitis complicated by Alcaligenes faecalis septicemia

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MEASLES, although seldom of serious consequence in its characteristic pattern, may have a variety of serious complications [1] Secondary bacterial infections are relatively common, but no cases have been reported of *Alcaligenes faecalis* septicemia as a complication. This bacterium is a normal intestinal saphrophyte, but it may invade body tissues to produce a variety of clinical patterns. It is a short, gram-negative bacillus which is weakly motile, possessing poorly developed peritrichal flagellae. First isolated by Petruschky[2] from stale beer, the bacterium was named for its ability to produce an alkaline reaction in certain media. It ferments none of the usual carbohydrates, does not form indol or liquefy gelatin, and is not agglutinated by polyvalent Salmonella sera. Litmus paper shows a strongly alkaline reaction, and a brown pigment is formed on potato media. Colonies resemble those of *Escherichia coli*, but are flatter, have a raised central portion, and a spreading undulant edge.[3]

CASE REPORT

Five days prior to admission, a 3½-year-old white girl with a history of recent exposure to measles had a sudden onset of fever, rhinorrhea, cough, and flushed facies. The following day an eruption appeared over the face and upper thorax, and frequent dark brown stools were noted. Three days later, the eruption was generalized, but the fever and diarrhea had subsided. On the day of admission, she ate poorly and was unusually drowsy. She was first seen in the emergency room in a generalized convulsion which subsided after intravenous administration of a barbiturate. A widespread petechial eruption was present with the heaviest distribution on the arms and abdomen. The pulse was 130 per minute, regular, and thready. The initial blood pressure was 140/110, but it soon fell to 100/60. Rectal temperature was 102.4° F. The conjunctivae were injected; the pupils were small, reacting poorly to light, and corneal reflexes were intermittently absent. A spinal tap revealed a cell count of 42 mononucleated cells per cubic millimeter, a sugar level of 66 mg. per cent, and protein of 82 mg. per cent. No microorganisms were detected by Gram's stain. The tentative diagnosis was hemorrhagic measles with encephalitis. A white blood cell count and differential were reported as 19,400 cells per cubic millimeter, 62 per cent polymorphonuclear leukocytes (17 nonfilamented), 34 per cent lymphocytes, and 4 per cent monocytes. Urinalysis showed 1 plus albumin and 2 plus acetone.

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Two blood cultures were obtained and penicillin-sulfadiazine therapy instituted. Except for another generalized seizure the patient's condition remained unchanged through the first night. Spinal fluid findings the following day were unaltered and the white cell count of the blood was 32,150 with polymorphonuclear predominance. The hemoglobin level which was 17.5 Gm. per cent initially had fallen to 11 Gm. per cent by the fifth day. The white blood cell and differential counts became normal on the fifth day. A roentgenogram of the chest was negative as were two additional urinalyses. Bleeding and clotting times were normal and serum agglutinations for Salmonella, Brucella, and Rickettsia were negative. On the fourth day growth was noted in both blood cultures, and the microorganism was subsequently identified as *Alcaligenes faecalis*. It was sensitive to all antibiotics tested except penicillin and streptomycin. Agglutination of this organism was positive in a dilution of 1:320 on the eighth and fourteenth days, respectively. Agglutination studies on a random group of white patients were negative. For the first 5 days the patient was unresponsive and disoriented; she did not recognize her parents. Her temperature fell slowly and was normal on the fifth hospital day. Prior to discharge she was an alert, talkative child with no apparent neurological sequelae.

DISCUSSION

Approximately 40 cases of systemic infection by *Alcaligenes faecalis* have appeared in the literature.[4-19] The majority have had a clinical pattern similar to that of mild typhoid.[4-10] Constitutional symptoms include slight chill, severe headache, anorexia, nausea and vomiting. Constipation or frequent yellow liquid stools may occur. Typically the temperature varies between 101° and 105° F. for 2 to 5 days, becomes normal, and then recurs. In one case urticaria appeared, but no other dermatological manifestations have been recorded.[9]

Blood cultures were positive for *Alcaligenes faecalis,* and agglutination titers varied from 1:60 to 1:1,500. Few deaths have resulted from these infections, but Ravenel[10] reported one case with postmortem lesions similar to those of typhoid fever. *Alcaligenes faecalis* was found in the spleen and intestinal ulcers. Symptoms may simulate those of other diseases such as infectious hepatitis, leukemia, bacillary dysentery, and rheumatic fever.[11] Endocarditis[12-14] and puerperal sepsis[15] have been reported. Central nervous system involvement has been reported in 11 cases.[16-19] Two instances of bacteremia and meningitis in the newborn were reported by Bischoff.[19] The organism may cause or be associated with localized disorders including gallstones,[20] renal stones,[21] cervical abscess,[22] and conjunctivitis.[23]

Why this girl with measles developed septicemia from *Alcaligenes faecalis* is, of course, purely speculative. Hirst[24] suggests that this saprophytic organism becomes pathogenic during intestinal disease. It is known that measles may cause a generalized lymphoid hyperplasia including swollen Peyer's patches[25]; such lesions may have offered an entrance for the bacteria.

SUMMARY

A case of measles encephalitis with *Alcaligenes faecalis* septicemia is presented. A review of the literature indicates the infrequency of systemic invasion by this organism. A mode of pathogenesis has been suggested.

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Intestinal obstruction in a child with a peritonealized urachal remnant

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INTESTINAL obstruction due to congenital anomalies is uncommon beyond the age of 1 year. Even less common is the occurrence of intermittent intestinal obstruction with complete disappearance of all symptoms between attacks.

The most common cause of intermittent intestinal obstruction in infants below the age of 1 year is intussusception.[1] The classical symptomatology of crampy abdominal pain, straining, and the passage of blood by rectum is almost diagnostic. Most of the remaining cases of intussusception occur in middle or late adult life, usually with a predisposing cause such as a polyp or intestinal neoplasm. The patient to be presented had symptoms suggestive of intussusception but had intestinal obstruction due to a heretofore unreported cause.

CASE REPORT

A 7-year-old white girl was hospitalized on Jan. 18, 1960, with the chief complaint of intermittent abdominal pain of 8 days' duration. The patient was in good health until this time except for the occurrence of an umbilical discharge noticed at birth which persisted to the age of 1 year. The discharge was nonpurulent and never recurred after the first year. Her growth and development were within normal limits. A history of allergy to food or inhalants in either the patient or the family was not elicited.

Approximately 8 days prior to admission, the patient suddenly developed severe, colicky, periumbilical pain. There was no radiation of the pain which was severe enough to cause the child to double up and scream. The pain disappeared as rapidly as it began and recurred about 8 times over a period of 2 hours. During this time the patient refused food and liquids but did not vomit. The colicky abdominal pain was not accompanied by diarrhea or the passage of blood or stool.

Physical examination shortly after the attack elicited moderate tenderness in the periumbilical area, but there were no other abdominal findings. The child was hospitalized. Examination of the stool was negative for occult blood and otherwise appeared normal in size and shape. A complete blood count, urinalysis, intravenous pyelogram, and barium enema were entirely normal. The attacks recurred while the patient was in the

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hospital, and the parents were advised that a laparotomy should be performed. This was refused and the patient was transferred to the Jefferson Medical College Hospital on Jan. 26, 1960.

Shortly after admission to the hospital, a similar attack of pain occurred. Almost immediately after the attack subsided, she was seen by a competent observer who performed a rectal examination and palpated a mass high anteriorly which disappeared shortly thereafter. There was no evidence of blood on the examining glove and the stool was negative for occult blood. A repeat blood count, urinalysis, and barium enema were again negative. A tentative diagnosis of transient ileocolic intussusception was made and the patient prepared for operation.

Fig. 1. *a*, Diagrammatic representation of findings at operation. The anterior abdominal wall is visualized from the peritoneal aspect. The arrow lies between the peritonealized urachal remnant and the peritoneum.

b, *c*, and *d*. Longitudinal and cross-sectional diagrams of possible stages in the development of the peritonealized urachal remnant.

Exploratory laparotomy was carried out on Feb. 1, 1960, through an infraumbilical transverse abdominal incision. The peritoneal cavity was opened and a tight, completely peritonealized band was noted to extend from the apex of the bladder to the umbilicus (Fig. 1, *a*). A portion of the omentum and the cecum dislodged from the urachal ring. This may have resulted from the relaxation provided by the general anesthetic. The band was completely removed, and the histologic diagnosis confirmed the clinical impression of a persistent urachal ring.

Following excision of the band, complete exploration of the abdomen was carried out which was found to be normal in all other respects. The appendix was normal in size and position, and was removed. The postoperative course was uneventful and the patient was discharged on Feb. 9, 1960. There has been no recurrence of symptoms since the time of operation.

DISCUSSION

The clinical picture presented by this patient was that of intermittent intestinal obstruction or ischemia. The presence of a tight, completely peritonealized urachal ring, could easily compress a loop of intestine against the abdominal wall, producing the symptoms described in the case report. A report by Cullen[2] published in 1916, classified many types of umbilical lesions that might be expected to produce such symptoms but the presently described lesion was not included. An extensive review by Trimingham and McDonald[3] and one by Cresson and Pilling[4] also failed to describe such a deformity.

Embryologically, the bladder is originally a tubular organ. After the second month of development, the epithelium-lined tube begins to expand with a tapering apex into an elongate urachus. The urachus is continuous at the umbilicus with the remnant of the allantoic stalk. The urachus loses its connection with the umbilicus after birth and is

drawn down by the descending bladder. The umbilical discharge from which this patient suffered up to the age of 1 year would lead one to suspect the presence of a persistent patent urachus. Ordinarily, the urachus is retroperitoneal and persists throughout life as a more or less patent canal about 5 cm. long. Fibrous bands, usually known as the middle umbilical ligament, connect the urachus with the umbilicus. Normally, this structure is retroperitoneal and therefore there is no possibility of a loop of bowel becoming wedged between it and the anterior abdominal wall. An excellent description of the development of the urachus is provided by Arey.[5]

In the case described in the article, the urachal band had become circumferentially peritonealized and thus a complete ring made up of the band and the anterior abdominal wall was present. It is possible that, as the child grew, the fibrous contraction of the urachal band may well have caused increased tension similar to that of a bowstring. A possible embryologic explanation of this is diagrammatically represented in Fig. 1, *b*, *c*, and *d*. In all probability, the symptoms described in the report were due to a loop of intestine becoming compressed between the urachal band and the abdominal wall.

SUMMARY

1. A patient with intermittent intestinal obstruction due to a completely peritonealized urachal ring is presented.

2. A possible etiological explanation of the mechanism of development of the urachal ring is given.

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TROPICAL PEDIATRICS

Indian childhood cirrhosis

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CIRRHOSIS of the liver among young children is world-wide but occurs rather infrequently in the temperate zones. There seems to be a greater prevalence of it in the tropics and subtropics. It is in India and the West Indies, however, that cirrhosis is sufficiently common in children between 1 to 5 years of age to constitute a public health problem. The Jamaican cases have been labeled veno-occlusive disease (V.O.D.)[1] because of the distinctive pathologic changes around the hepatic venous tributaries. The majority of cases in India in this age group have been diagnosed as infantile biliary cirrhosis since Gibbons[2] in 1888 drew attention to the proliferated bile ducts in the few autopsy specimens he studied. This term was a misnomer, however, since further studies have revealed that this proliferation of the bile duct is not present in the earlier stages or in all autopsy specimens. Most of the cases reported in Indian literature occur in young children rather than in infants; hence the term "infantile" is inappropriate. The term "Indian childhood cirrhosis" is used in this article to refer to those cases commonly found in India chiefly between the ages of 1 and 5 years. This term may be misleading, however, in that it may convey the idea that there are distinctive clinical or histologic features which distinguish the Indian cases from similar stray cases of cirrhosis of indeterminate cause in children of this age group in other parts of the world, as, for example, the 13 of the 98 cirrhotic children in a 30-year period at Boston reported by Craig and associates.[3] This does not seem to be warranted (videinfra). However, with all these limitations, the term Indian childhood cirrhosis seems noncommital in referring to the frequently occurring childhood cirrhosis of indeterminate origin seen in India.

Although this condition was reported in the Indian Literature for over 70 years, the

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first authentic record in English was by Sen[4] in 1887; the etiology and pathogenesis of this condition have yet to be established. In the present investigation, we have been able to draw some broad generalizations based on a comprehensive clinical, epidemiologic, and histopathologic study carried out during the last 9 years in the Liver Clinic of the Pediatric Department of the General Hospital, Madras, South India.

MATERIALS AND METHODS OF STUDY

The cases included in this study as hepatic cirrhosis and persistent hepatitis (supported in most instances by histologic studies of liver obtained by needle biopsy) were all from this clinic at Madras during 1950 to 1958 and could be classified as follows: (1) 6 cases of neonatal hepatitis similar to cases reported elsewhere in the world; (2) 4 cases of biliary cirrhosis following congenital atresia of the bile ducts in infants and similar to ones reported in other parts of the world; (3) 166 cases of cirrhosis with insidious onset and persistent hepatitis, with no discoverable antecedent cause, mostly in the age group 1 to 5 years, for which we would prefer to use the noncommital term Indian childhood cirrhosis (videinfra for description of the clinical and pathologic aspects); (4) 118 cases of hepatomegaly and symptoms similar to those of the previous group occurring after an initial or antecedent episode of jaundice and malaise (posthepatitis cirrhosis); and (5) 16 cases which we would label "nutritional fibrosis," which is characterized by hepatomegaly with evidence of marked fibrosis and prominent fat vacuolation in the liver as studied in biopsy sections. We have not encountered fat vacuolation in the liver to an appreciable degree in the other groups described above. Those in the latter group have had a benign course, improving in general appearance and histologically when fed a high protein diet. They did not have jaundice at any time and did not exhibit low-grade febrile episodes (not attributable to a discoverable infection) which is a feature of the Indian childhood cirrhosis and posthepatitis groups. They all had some minor evidences of nutritional deficiencies though none of them have had frank kwashiorkor.

There are also included in the study the following groups of patients who were followed clinically, aided by histopathologic examination of liver biopsy specimens in many cases: (1) observation for 1 to 4 years of 236 children first observed during 1954 to 1956 with what appeared to be endemic hepatitis, probably viral in origin; (2) observations for periods of 3 to 9 years of 36 children originally suffering from florid kwashiorkor; (3) examination and follow-up of 121 asymptomatic siblings of children with cirrhosis, persistent hepatitis, or acute hepatitis (liver biopsy was obtained when the initial or follow-up examination indicated likelihood of pathologic changes in the liver, with a view to detect the early stages which

Fig. 1. Two-year-old child in early stage of Indian childhood cirrhosis. Note enlarged liver which is firm with a sharp-edge outlined. Symptoms were impaired appetite, decreased activity of insidious onset, and occasional low fever of 2 months' duration; there was no jaundice. Liver biopsy showed a histologic picture of persistent hepatitis.

Fig. 2. Three-and-one-half-year-old child in the advanced stage of Indian childhood cirrhosis with ascites and prominent abdominal veins.

may lead to hepatic cirrhosis of insidious onset in siblings, and special attention was given to those with asymptomatic hepatomegaly); (4) study of a small series of 8 patients with congestive splenomegaly due to extrahepatic causes—the clinical diagnosis was aided by a splenogram in some cases and in others a splenectomy with or without splenorenal shunt was performed; and (5) a review of the case records of 204 infants with congenital syphilis treated in the last 3 years (liver biopsies from 31 of these patients were made available to us by Drs. Rajam and Rangiah).

The liver biopsy specimens, obtained mostly with the use of a Vim-Silvermann needle, were fixed in 10 per cent formalin and processed through paraffin. The sections were stained by hematoxylin and eosin and by Gomoris reticulum stain. There were also 11 autopsy specimens of livers from the different groups.

OBSERVATIONS

The vast majority of cases of cirrhosis and of persistent hepatitis syndrome in infancy and childhood seen in Madras, not including the few cases of neonatal hepatitis, cirrhosis following biliary atresia, and other miscellaneous groups, seem to fall into two main groups. First are those who seem to have developed the condition after an episode of jaundice clinically resembling viral hepatitis. Forty per cent of these cases (118 out of 284) in the present series belong to this category. We would designate these as "posthepatitis" patients without committing ourselves definitely to the nature of the etiologic agent. In many of these, the initial episode of jaundice was followed by a variable quiescent period during which the patients were asymptomatic and free

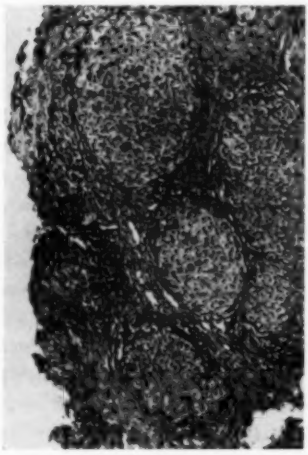

Fig. 3. Needle biopsy specimen of liver of child with Indian childhood cirrhosis in well-established stage. Note islands of regenerating parenchyma encircled by excessive amounts of cellular and fibrous connective tissue. Proliferation of the bile duct is not conspicuous. (Hematoxylin and eosin. ×180; reduced approximately ⅓.)

from jaundice for months or years. This was followed by recurrence of jaundice, hepatomegaly, low-grade fever, digestive symptoms, peevishness, and other manifestations of chronic hepatitis. In some, however, the initial jaundice never disappeared but deepened with development of slight general anasarca, which was, in all probability, because of the poor synthesis of albumin by the diseased hepatic parenchymal cells. The general condition deteriorated rapidly in the course of 2 or 3 months after the onset of the initial illness. We class such cases as "malignant hepatitis." In the second group of 166 (60 per cent) cases the history was quite different. Initially there were vague symptoms of abdomenal distention due more to the mild tympanitis than to the moderate enlargement of liver present at this stage, peevishness, altered appetite, and frequently some low-grade fever (Fig. 1). As the disease advanced, the appetite diminished still more, the spleen was often enlarged as the liver became firmer, and there were periods of low-grade fever without any discoverable infection. Ascites due to portal obstruction was present in the advanced stages (Fig. 2). Jaundice was noticeable in some of the advanced cases, but slight icterus could be made out in some at any stage, especially during the febrile periods. The course was variable, some recovering slowly with relapses over a period of several years, although the majority of cases which developed ascites deteriorated rapidly and died of hematemesis, intercurrent infections, or hepatic coma. The duration of illness in fatal cases was a few months to a few years. There was nothing remarkable or contributory in the histories of the first year of life of these children.

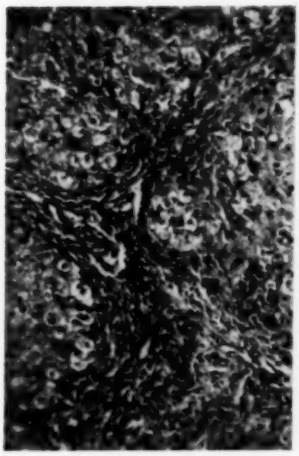

Fig. 4B. Needle biopsy specimen of same liver 4 months later. Notice the increased hepatic damage. Highly cellular fibrous tissue bands are seen with attempt at pseudolobule formation. (Hematoxylin and eosin. ×360.)

Fig. 4A. Needle biopsy specimen of liver of patient with Indian childhood cirrhosis in very early stage. There was a history of impaired appetite and slight abdominal distention of only a month's duration; the child ultimately died of cirrhosis 14 months later. This photomicrograph illustrates acute hepatitis with a moderate degree of swelling of the liver cells. (Hematoxylin and eosin. ×300; reduced ⅓.)

While the term "cirrhosis" was appropriate in many of these cases on clinical and histologic data, some in both of the above groups have been labeled "persistent hepatitis." The main features of persistent hepatitis are as follows: continuing presence of vague digestive symptoms like anorexia, distention of abdomen, and often repeated low-febrile episodes not attributable to intercurrent infections, but possibly due to recurrent damage of the liver cells. The liver is enlarged and firm in consistency, often with a sharp margin. Lack of liveliness or actual peevishness are invariably noticeable, presumably due to liver disfunction, but ascites and other signs of portal hypertension are not present at this stage. Histologically there are multiple foci of damage of the liver cells and intralobular cellular infiltration. The reaction of fibrous tissue is not prominent and the lobular architecture is still preserved at this stage, whereas in cirrhosis there is marked fibrosis with pseudolobules and distortion of architecture. This composite clinical and histologic picture for which we prefer the term "persistent hepatitis" was found in large numbers, both in the group with insidious onset and in the group which had a history of jaundice either at the onset or previous to the illness. Some of these children recovered after several months, but a good proportion of them went on to the final stage of cirrhosis with signs of portal hypertension and hypersplenism. Jaundice might or might not have been present at either stage.

Comparison of data from cases of cirrhosis or persistent hepatitis of insidious onset and from similar cases following an episode of jaundice resembling viral hepatitis as well as data obtained from cases of acute hepatitis and hepatic coma are presented in Table I.

It is apparent that in all 4 groups over two-thirds of the cases fall into the age group of 1 to 3 years.

Indian childhood cirrhosis and persistent hepatitis of insidious onset. Of the 166 children without any previous attack of jaundice studied in the past 8 years, 73 (44 per cent) died of the complications of cirrhosis and 20 are not traceable and are presumed to be dead. Forty (24 per cent) of the survivors have minimal or no symptoms at this time (the term "cure" is avoided in this disease). Some of the survivors have been receiving gamma globulin on a therapeutic trial basis.

Persistent hepatitis and cirrhosis with a history of antecedent jaundice. The 118 cases in this group revealed a pattern similar to that of the insidious onset group; 46 per cent are dead and about 25 per cent seem

Table I. Age and socioeconomic status* of children with Indian childhood cirrhosis, posthepatitic cirrhosis, acute hepatitis, and hepatic coma in Madras

	Indian childhood cirrhosis and persistent hepatitis of insidious onset (1950 to 1958)	*Posthepatitis cirrhosis and persistent hepatitis (1950 to 1958)*	*Endemic hepatitis—acute stage (1950 to 1958)*	*Hepatic coma (emergency admissions in last 2 years)*
No. of cases	166	118	607	30
Below 1 year of age (%)	2	2.5	0.6	13.0
1 to 3 years (%)	67	67	61	70
3 to 10 years (%)	31	30.5	38.4	17
Upper class (%)	5	2	2	6
Middle class (%)	94	96.7	96.7	94
Lower class (%)	1	1.5	1	nil

*About 1 per cent of the population of Madras is in the upper class, 70 per cent are in the middle class, and 29 per cent are in the lower class (as culled from the profession tax returns of the Corporation of Madras).

Table II. Follow-up of 236 children with endemic hepatitis observed in the acute stage during 1954 to 1956

Recovered and well to date	138	(59%)
Persistent hepatitis or cirrhosis	35	(15%)
Residual symptoms (post-hepatitis syndrome)	38	(16%)
Died of hepatic coma in acute stage	6	(2%)
Died of complications of cirrhosis	19	(8%)

to have recovered with minimal residual symptoms.

Individual cases of both types of onset manifested alterations in their course; relapses were associated with low-febrile bouts and increased peevishness with or without icterus.

Endemic hepatitis cases. Of the 607 children with symptoms and signs of acute hepatitis seen during 1950 to 1958, 236 were encountered during 1954 to 1956 (Table II).

Posthepatitis syndrome. During the follow-up of children with acute hepatitis, some continued to exhibit vague digestive symptoms and a slightly enlarged liver. The liver was not particularly firm but revealed minimal histologic changes such as balloon cells and a few infiltrates, mainly periportal, for several months after the initial episode. Such livers are vulnerable to further damage, though recovery is the rule. Persistent hepatitis is a much more definite and pronounced clinical state with symptoms of liver dysfunction, firm hepatomegaly, and characteristic histologic changes. Of the 54 patients who, during follow-up from the early stages of jaundice, were found to have these chronic sequelae or cirrhosis, 40 (75 per cent) developed such sequelae within 6 months after the initial attack.

Histopathology of the liver in Indian childhood cirrhosis. In the *late* cases of childhood cirrhosis of insidious onset, histologic changes were similar to those reported by other workers with minor differences. Liver biopsy or autopsy specimens showed the characteristic features of posthepatitic or postnecrotic cirrhosis. Parenchymal regeneration with nodular hyperplasia and progressive increase of fibrous tissue were present (Fig. 3). The mesenchymal reaction is composed of proliferating fibroblasts along with an increase of reticulin and collagenous fibers. Occasionally the fibrosis is more diffuse, with a "basket-like" network of fibers spreading between the parenchymal cells. Foci of parenchymal destruction may or may not be seen at this late stage, although areas containing large degenerating balloon cells are frequently seen. Fatty changes are conspicuously absent. Proliferation of the bile duct was seen in only a few of the specimens. There was no evidence of inflammatory changes within or around the bile ducts. As reported by several workers,[5] the biliary system does not appear to be primarily involved. Likewise we also failed to detect any marked occlusive changes in the radicals of the hepatic venous tree as pointed out earlier

Fig. 5. Needle biopsy specimen of liver of child with Indian childhood cirrhosis (stage of chronic hepatitis). There was a history of hepatomegaly and symptoms of 5 months' duration. Heavy cellular infiltrates (portal and intralobular) and variations in size of hepatic parenchymal cells indicate persistent hepatitis. (Hematoxylin and eosin. ×250; reduced approximately ¼.)

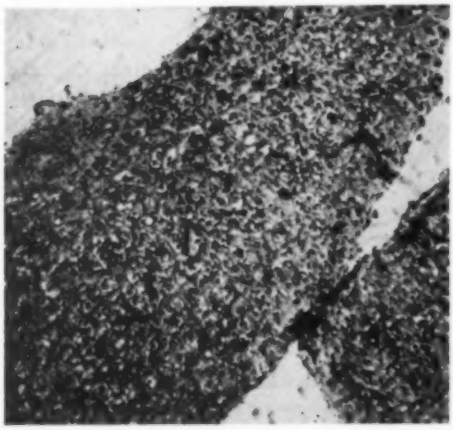

Fig. 6. Needle biopsy specimen of liver obtained from a 4-year-old child with acute hepatitis. The patient had had a mild febrile illness with slight jaundice of 3 weeks' duration suggestive of acute endemic hepatitis. Note the intralobular infiltrates and swelling of hepatic parenchymal cells with nonfatty vacuolation which are manifestations of acute hepatitis. (Hematoxylin and eosin. ×240.)

by Aikat[20] and by Achar and Chacko.[6] This fact is being re-emphasized because of the recent observations of Jelliffe, Bras, and Mukherjee[7] to the contrary in some of their series in Calcutta.

More interesting changes were observed in the very *early cases* with both types of onset as well as in some of the apparently healthy siblings of such, however. Irrespective of the mode of onset, similar histologic changes were observed at comparable stages. These were again similar in many respects to the sequence of histologic changes reported in adult cases of viral hepatitis.[8, 10] The liver biopsy specimens in the early cases (Fig 4A) showed a picture clearly resembling viral hepatitis in the acute stage in the adult. There was mild, moderate, or even severe degree of swelling of the liver cells, either in scattered areas or more diffusely, associated with periportal and intralobular cellular infiltrates. The swelling might progressively increase producing considerable rarefaction of the cytoplasm. Such cells are often referred to as "balloon cells." The cellular infiltrates were predominantly mononuclear, although in the very early stages a few eosinophils were also seen. At this stage the reticular framework of the liver was practically unaltered, an important feature for the subsequent orderly regeneration during the subsiding phase of hepatitis. Very occasionally intra- or extracellular acidophil bodies were seen which probably represent altered cytoplasmic remnants of liver cells. Pigmentary changes such as accumulation of lipofuscin, free or in the Kuppfer cells, mentioned as one of the features of acute viral hepatitis by Smetana[8] were only seen in a few cases.

When the liver biopsies were performed some weeks after the onset of symptoms, appearances suggestive of subsiding hepatitis were sometimes seen. The liver cells were swollen and showed considerable rarefaction of cytoplasm with pyknotic nuceli. This type of vacuolation was distinctly different from accumulation of fat seen in nutritional disorders of the liver. In spite of such extensive degenerative changes, signs of active destruction of the liver cells were absent. Intralobular cellular infiltrates disappeared at this stage, although the periportal cellular

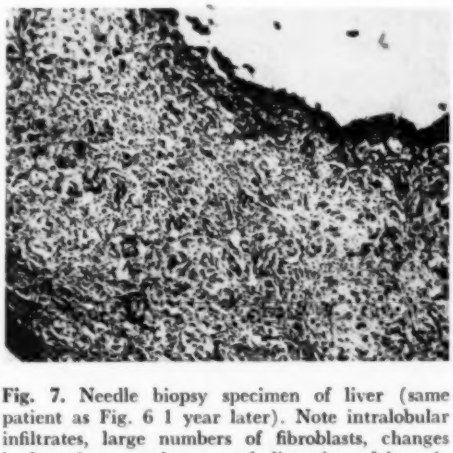

Fig. 7. Needle biopsy specimen of liver (same patient as Fig. 6 1 year later). Note intralobular infiltrates, large numbers of fibroblasts, changes in hepatic parenchyma, and distortion of hepatic architecture (persistent hepatitis). (Hematoxylin and eosin. ×240; reduced slightly.)

Fig. 8. Needle biopsy specimen of liver of patient in Figs. 6 and 7 several months later. Note the transition to posthepatitic cirrhosis (increased fibrous tissue with pseudolobules). This child subsequently improved clinically. (Hematoxylin and eosin. ×240; reduced slightly.)

infiltrates continued to persist in some cases. The reticular framework of the liver was practically unaltered. Such histologic changes were seen in cases with both types of onset as well as in apparently healthy siblings. Though of relatively good prognosis, evidences of subsiding hepatitis might persist long after the initial onset of the illness. It is not unlikely that such partially damaged or diseased liver cells become more vulnerable to superimposed secondary systemic infections or to further episodes of destruction of the liver cells by a process of antigen-antibody disturbance as postulated by Mackay and colleagues.[18] Otherwise, this stage is followed by regeneration of liver cells leaving no vestiges of past damage.

As pointed out, quite a large proportion of cases in both groups suffered from the syndrome of persistent hepatitis. The liver biopsies in such cases showed evidence of a continuing parenchymal destruction (Figs. 4B, 5, and 7). Multiple foci of liver cell necrosis were recognizable by the heavy intralobular cellular infiltrates. The character of the mesenchymal cells was also altered; in addition to mononuclear cells, large numbers of fibroblasts were seen. The periportal mesenchymal cells also showed further evidence of differentiation and organization. Special stains for connective tissue showed an increase of reticulin fibers around the portal tracts and also within the lobules. Irrespective of the mode of onset, quite a large proportion of cases with persistent hepatitis merges imperceptably into the final stage of cirrhosis. The cirrhosis was most often of the posthepatitis type (uniformly small pseudolobules), although occasionally a postnecrotic type of cirrhosis was seen resembling classical coarse nodular cirrhosis, especially in the autopsies or in wedge biopsy specimens. It was not unusual to find a composite picture in one and the same specimen. Follow-up of individual cases with the help of serial liver biopsies at intervals of months revealed a transition from one stage of hepatitis to another or eventually cirrhosis (Figs. 4B, 6, 7, and 8). There were also isolated cases which, after passing through a stage of florid cirrhosis, gradually recovered clinically with reversal of fibrosis

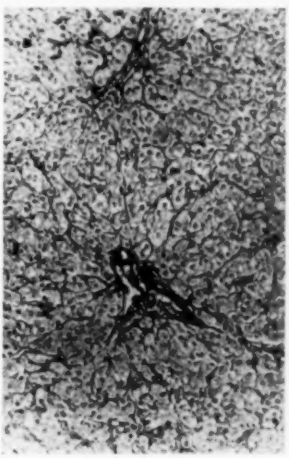

Fig. 9. Postkwashiorkor follow-up needle biopsy specimen of liver from a child who had florid kwashiorkor 4 years previously and who has remained on a poor protein diet. The liver is essentially normal (Gomori's reticulum).

in repeat hepatic biopsy studies, which suggests the occasional possibility of spontaneous reversal. Such reversal was more often seen in the series in whom gamma globulin was used therapeutically as described elsewhere in a separate article.[24]

It is interesting to note that multinucleated giant cells which were found in the livers in the few cases of neonatal hepatitis included in this study were not a feature of Indian childhood cirrhosis or of post hepatitis as seen in our series. Neither were they seen in the livers of children with congenital syphilis and hepatomegaly with histologic evidences of hepatitis (vide infra).

Fig. 10. A 9-year-old child with an enlarged and rather firm liver, slight ascites, and changes of skin on the legs due to malnutrition (nutritional cirrhosis). This child improved considerably with good diet and is now well.

We do not know the significance of this negative finding.

Studies on siblings. A history of hepatic disorders in siblings was obtained in a significant proportion of patients with cirrhosis of the liver of insidious onset and in those with endemic hepatitis and its sequelae. Often both conditions were seen in the same family (Table III).

Of 121 asymptomatic siblings of children with Indian childhood cirrhosis or post-hepatitis cirrhosis, 50 had hepatomegaly. In 22 of them a liver biopsy was obtained and revealed pathologic changes indicative of hepatic damage in various stages. During a period of 2 years, 13 developed clinical and histologic evidence of persistent hepatitis with a transition to cirrhosis in one.

In a significant proportion of the children with acute hepatitis (20 per cent), there was also a history of a similar episode of jaundice among the adult members of the family, either concurrently or in the recent past. These data suggest that childhood cirrhosis of insidious onset and acute endemic hepatitis occur together in significant numbers among siblings and that there is a significant incidence of acute hepatitis among adult members in their families. Thus a close relationship and a possible common cause are suggested. There was no indication whatsoever of ingestion by these children or by other members of their families of hepatotoxic substances such as the alkoloid bush tea of Jamaica. In the cases studied at Madras, the possible role of such factors would appear to be nonexistent.

Follow-up studies of children with kwashiorkor. In an attempt to find out if kwashiorkor leads to cirrhosis, 36 children were followed clinically and by serial liver biopsies at frequent intervals after the original episode of kwashiorkor (2 for 8 years, 16 for 6 years, and 18 for 4 years).[17] None of them showed clinical evidence of cirrhosis. Though there were mild periportal scars and the liver cells frequently showed rarefaction due to the poor protein diet on which they were reared, there was no progressive increase of

fibrous tissue or appearance of pseudolobulation and other characteristics of cirrhosis in the study of serial liver biopsies (Fig. 9). Only one showed appreciable fibrosis in the liver 4 years after discharge for kwashiorkor. This fibrosis, however, regressed subsequently and the child at no time had clinical symptoms of cirrhosis. All of these 36 children have been reared on the usual protein-poor diet which is customary for poor families, and they received very little milk but some pulses (leguminous plants). The only period when they had adequate animal protein was during hospitalization for kwashiorkor.

Fatty liver disease with fibrosis. From among a large number of children with abnormally large livers seen in our liver clinic during the past 9 years, we have been able to diagnose 16 cases of "nutritional fibrosis" on the basis of the finding of appreciable fibrotic or cirrhotic changes in the liver with conspicuous fatty vacuolation of the liver cells in the needle biopsy specimens (Figs. 10 and 11). As mentioned, appreciable fat vacuolation was not encountered in the posthepatitic cirrhosis specimens or in those of the large group of children with insidious cirrhosis. Patients with nutritional cirrhosis did not have jaundice and were apparently lively in spite of the hepa-

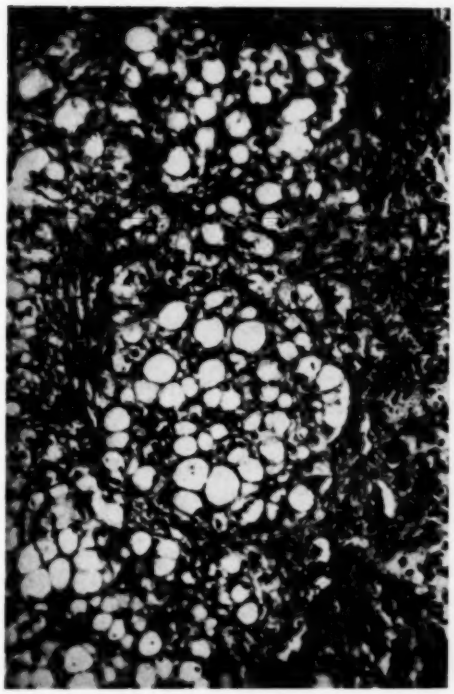

Fig. 11. Needle biopsy specimen of liver from the same girl as in Fig. 10. Marked fat vacuolation with cellular and acellular connective tissue formation indicates nutritional fibrosis. Hepatic changes regressed appreciably after months of a high protein diet along with clinical improvement. (Hematoxylin and eosin. ×360.)

Table III. History of hepatic disorders in siblings of children with endemic hepatitis and cirrhosis*

Group	*Total No.*	*No. with siblings having acute hepatitis or posthepatitis cirrhosis*	*No. with siblings having insidious onset of cirrhosis liver*	*No. with siblings having acute hepatitis and Indian childhood cirrhosis in the same family*
A. Acute hepatitis and post-hepatitis cirrhosis or persistent hepatitis	725	62	25	8
B. Insidious onset of persistent hepatitis or cirrhosis of liver	166	16	12	5

*In many instances more than 1 sibling in the family were involved with one or the other of these conditions.

tomegaly. Most of them were in an older age group (over 5 years of age) however. Often coexistent nutritional deficiencies were discernible in the skin, eyes, and mucous membranes, though none of them had had frank kwashiorkor. Most of these children improved with a diet liberal in protein. Their clinical features, histologic appearance of the liver, as well as their benign course, of their disease, distinguish them from the much larger number of patients with Indian childhood cirrhosis.

Hepatic changes in congenital syphilis. Review of the case records of 204 infants with active congenital syphilis treated in the Institute of Venerealogy, General Hospital, Madras, during 1955 to 1957 revealed hepatomegaly in 69 of them (37 per cent) but clinically evident jaundice in only 2 (1 per cent) (Sowmini[22]). Histopathologic study of the liver biopsy material from 31 of these infants with active congenital syphilis and hepatomegaly was undertaken by Drs. Rajam and Rangiah who permitted us to review the slides. We did not find appreciable mesenchymal changes in these livers except in one (videinfra), though we found changes suggestive of subsiding hepatitis. The so-called pericellular fibrosis in the liver ascribed to congenital syphilis was seen in only one infant 1 month old and biopsied a day before he died. This poses the question whether pericellular fibrosis of the liver in congenital syphilis is only a feature of overwhelming prenatal syphilis resulting in stillbirth and is not ordinarily encountered in live infants (Rajam[23]). Some cases in this series were re-examined a year after successful treatment. There was no hepatomegaly. Hepatic tissue from 3 of these patients obtained by needle biopsy had a normal appearance without any appreciable fibrous tissue formation.

DISCUSSION

From the above data it would appear that childhood cirrhosis, persistent hepatitis, and endemic acute hepatitis are all common in Madras and occur preponderantly in the age group of 1 to 5 years. It might be argued that the children with an initial or antecedent episode of jaundice, referred to in this series as acute hepatitis, might be cases of jaundice due to other causes. We have relied on a consideration of the clinical features and exclusion of other causes of jaundice in this age group, supported by a study of the liver histology in many, before making the diagnosis of acute hepatitis of possible viral origin. These cases have been encountered throughout the year; there was no history of previous injections (immunizations, except against small pox, are not in vogue) or of transfusions in the vast majority, thereby excluding serum hepatitis. Though tests of hepatic function could not be done as a routine for want of sufficient facilities, study of the anatomic structure of the liver in these acute hepatitis cases has revealed many features usually found in the acute stage of viral hepatitis. Swelling or shrinkage of liver cells with great variations in size and shape giving rise to alterations in the hepatic architecture and portal and intralobular infiltrates in varying degrees were features found in most of the biopsy specimens. Acidophilic bodies and lipofuscin pigment were seen only in a few. Although the reticular framework was usually well preserved, collapse and condensation of argentophilic fibers in some areas (the feature referred to by Smetana[8] as one of the characteristics of viral hepatitis in the acute stage) were seen in a few. It is interesting to note that Soedjono and coworkers[19] confirmed histopathologically the clinical diagnosis of viral hepatitis in the acute stage in only 33 of 68 children in Djakarta. The hepatic parenchymal cells in our series of acute hepatitis showed a peculiar rarefaction in biopsy studies in most of the cases which can be attributed to many noxious influences including suboptimal protein diets. There are many causes of acute hepatitis—viral, spirochetal, protozoal, and toxic agents—each with its own individual clinical features and anatomic conditions of the liver, but there seems to be some histologic features in the liver common to many of these agents. It is interesting to note that

many of the infants with active congenital syphilis and hepatomegaly showed histologic changes in the liver on biopsy (Fig. 9) similar to those described as characteristic of subsiding hepatitis (Fig. 5). Infectious mononucleosis can produce changes in the liver suggestive of acute hepatitis, but has been excluded from this series on clinical grounds. Miscellaneous conditions (bacterial infections and other systemic diseases) have also been known to cause nonspecific reactive hepatitis. However, consideration of the history, clinical features, and the liver histology has served to eliminate the above mentioned miscellaneous causes from this series. Toxic agents are possible factors in some of the cases in this series, though we have failed to elicit a history of ingestion of toxic substances in the diet or as medicaments in any of our series, and histologically we have not encountered the necrosis in the central zones of the hepatic lobules commonly described in such poisoning. Thus it appears that endemic hepatitis prevalent among children in Madras resembles infective hepatitis in many respects, except that no explosive outbreaks of the former have thus far occurred in a community. Whether the causative agent of endemic hepatitis in Madras is identical with the infective hepatitis virus is a question that probably can be answered definitely when laboratory methods of isolation or identification of infective hepatitis virus or serologic tests become available or if experiments on human transmission are performed. Experiments conducted in our department[21] designed to transmit the disease to canine pups by inoculating them with suspensions of liver biopsy material obtained from patients with Indian childhood cirrhosis, persistent hepatitis, and acute hepatitis have been unsuccessful. Attempts to infect 10-day-old chick embryos with a saline suspension of liver biopsy material from such cases also have failed so far. These failures do not, however, negate the possible viral cause of Indian childhood cirrhosis, because known hepatitis-producing viruses in man (A, B, and infective mononucleosis) have so far not been transmitted to animals or chick embryos.

There is close similarity in the evolution of the histologic features in the liver in childhood cirrhosis of insidious onset without a discoverable antecedent cause and that following an episode of jaundice suggestive of acute endemic hepatitis. This is evidenced by the histologic findings of acute hepatitis, persistent hepatitis, and postnecrotic cirrhosis at comparable stages in both conditions, and inclines us to the opinion that both of these conditions have a related, if not an identical, cause. Aikat and Srivatsava's[20] observations on cases of childhood cirrhosis in Gwalior in Central India are similar to ours; a large number of their cases had an insidious onset, and a small number followed an acute episode of jaundice. Though there are some who think that cirrhosis is an uncommon if not an unrelated sequel to viral hepatitis (Smetana[9]), many reports[10, 11, 12] emphasize the increasing frequency with which cirrhosis follows viral hepatitis. It is well known that there can be considerable variations in the severity and mortality during the acute episode of viral hepatitis in different epidemics and endemics. A perusal of available literature shows that, in general, infective hepatitis has changed in its severity and in its epidemiologic conditions during the past 50 years. It is possible that strains of hepatitis producing viruses other than A and B exist. It is also well known that anicteric cases can produce as severe sequelae as the icteric ones. In the light of these considerations we think that in Madras, at any rate, infective hepatitis-like disease is endemic and an appreciable number of such cases have developed cirrhosis. Some of our cases with insidious onset of cirrhosis have been followed from early stages when they had a histologic picture of acute hepatitis to the stage of persistent hepatitis, clinically and histologically, and have finally ended in cirrhosis (Fig. 4). These could very well be anicteric forms. We are unable to offer an explanation for the relatively low incidence of this type of childhood cirrhosis in other

parts of the world or even in the neighboring tropical countries as compared with India. However, the clinical and histologic features of cirrhosis with insidious onset of indeterminate origin described by Craig and associates[3] are not different from the cirrhosis of similar insidious onset found in large numbers in Madras and other parts of India. The difference is in numbers, there being only 13 cases in Boston in a period of 10 years. While we have been able to follow some cases from the stage of acute hepatitis to persistent hepatitis and to cirrhosis, we are not able to find a satisfactory explanation as to why this should occur frequently in our series.

We have considerable circumstantial evidence that in the pathogenesis of Indian childhood cirrhosis malnutrition is not the main initiating factor, in spite of the fact that protein deficiency conditions like kwashiorkor and milder states are quite common in Madras in the same age group. But these occur in the poorest socioeconomic classes in whom the occurrence of Indian childhood cirrhosis is rare in our series and even endemic hepatitis is infrequent (Table I). Although not optimal, the dietetic histories of the patients with Indian childhood cirrhosis and persistent hepatitis reveal better intakes of calories as well as of protein than are obtained by children in the very poor families from which the patients with kwashiorkor come. We have not encountered appreciable fat vacuolation in the liver in our series of Indian childhood cirrhosis and persistent hepatitis while such vacuolation is invariable at some stage or other in the livers of patients with kwashiorkor. None of the discharged kwashiorkor patients followed over years have developed cirrhosis. Thus the vast majority of cirrhosis cases in our series at Madras are not directly related to states of protein deficiency. It is a moot point whether suboptimal diet has any contributory role in the pathogenesis of Indian childhood cirrhosis. If so, the paucity of Indian childhood cirrhosis among the grossly malnourished children must be explained. The problem of adult cirrhosis, vis-à-vis protein malnutrition, is in a different category because of the long duration of malnutrition in adult cases.

The role of intercurrent infections is not clear. The auto immunologic mechanism described by Mackay[18] might be the explanation for the continuing or recurring damage to the hepatic parenchyma in these cases, though we have not been able to demonstrate the LE cell in the blood in the few cases studied. The LE cell has been found in some of the reported series of chronic active hepatitis.

Studies on asymptomatic siblings with hepatomegaly, some of whom eventually developed cirrhosis, have revealed that siblings of patients with endemic hepatitis may develop Indian childhood cirrhosis insidiously and vice versa. This observation together with similarities in the histologic pictures leads us to postulate that Indian childhood cirrhosis and endemic hepatitis are related. The undoubtedly significant familial incidence of Indian childhood cirrhosis might be due to genetic influences or to the same environmental factors operating on siblings. We are inclined to the latter possibility. Familial types of cirrhosis are rare anywhere in the world. Derangement of copper metabolism results in hepatolenticular degeneration and has been recognized in recent years as a cause of hepatic cirrhosis in children even without neurological manifestations. We have not been able to definitely exclude this in all the cases in this series due to lack of facilities for appropriate investigations, but in recent months we have been able to perform the serum oxidase activity screening test in a series of 10 cases of Indian childhood cirrhosis through the courtesy of Ortho Research Foundation, Raritan, New Jersey, who have supplied the screening kit. The test has been negative in the 10 cases in which it was performed, indicating normal ceruloplasmin levels in the blood.

We do not think any of our cases of childhood cirrhosis and chronic hepatitis could be attributed to congenital syphilis because

their serologic tests have been consistently negative.

Though there are certain similarities between the commonly occurring childhood cirrhosis in India and the equally common hepatic cirrhosis in the West Indies, which include the high incidence of each in the age group of 1 to 5 years and the generally poor protein diets of the majority of children in both regions, there are some striking differences. The type of initial acute abdominal swelling due to sudden hepatomegaly and ascites which subsides and is later followed by persistent hepatomegaly in the Jamaican cases is not a feature of the Indian cases. The histologic picture of exudation and hemorrhage around the small and medium-sized branches of the hepatic veins and in Disse's space in the liver found in biopsy studies in the acute stage of the Jamaican cases is distinctive. This has not been seen by us in any of the Indian cases, neither did we find such marked obliterative subendothelial formation around the small and medium-sized branches of the hepatic veins as is seen in the chronic stage in the Jamaican cases.[14] The hepatic changes in the cases in West Indies are now believed to be caused by poisonous elements in plants commonly used in herbal infusions in vogue there. Careful inquiries in our series in Madras have failed to reveal possible hepatotoxic agents in diets or in medicaments. For these reasons we think the two conditions are different in regard to etiology and pathogenesis.

Some of the patients in our series may have had so-called "congestive splenomegaly," though we have tried to separate this group by the clinical criteria of early splenomegaly, hematemesis, and signs of portal obstruction coming on before symptoms of hepatic dysfunction. The finding of a firm liver in the early stages of Indian childhood cirrhosis with parenchymal and mesenchymal changes in the needle biopsy studies has served as an additional aid to separate the two groups. Splenograms in selected cases have also been helpful.

It is possible that in some of our patients with Indian childhood cirrhosis multiple etiological factors are operative. The possibility of viral hepatitis has been discussed. Umbilical sepsis in the newborn period is commoner in India and neighboring countries than in the West and may result in thrombosis of the portal vein or of its radicals with resultant congestive splenomegaly. The contribution of suboptimal nutrition in the evolution of cirrhosis due to other causes is still not clear though assumptions are made. We are not in a position to give data about the occurrence of posthepatitic cirrhosis in young girls reported by Kunkel[15] and Sherlock,[16] since our pediatric clinic accepts children only up to 10 years of age; from published data, there does not seem to be a significant incidence in India.

The data presented permit us to surmise that Indian childhood cirrhosis is a form of chronic hepatitis possibly due to a viral infection akin to infective hepatitis.

SUMMARY AND CONCLUSIONS

1. Observations are recorded from a clinical study with the aid of serial liver biopsies in many of 284 children with Indian childhood cirrhosis or persistent hepatitis and of 236 children with "acute endemic hepatitis" resembling viral hepatitis.

2. Histologic evidence of acute hepatitis, persistent hepatitis, and postnecrotic cirrhosis have been found at comparable stages in the evolution of Indian childhood cirrhosis. Such changes have been observed in those with an antecedent history of jaundice suggestive of acute endemic hepatitis and those without such a clinical pattern.

3. There is a significantly high incidence of hepatic disorders in siblings of patients with endemic hepatitis and cirrhosis.

4. Follow-up studies of children who have recovered from kwashiorkor, from hepatomegaly due to active congenital syphilis, and from nutritional fibrosis were carried out to determine whether such conditions might participate in the pathogenesis of Indian childhood cirrhosis.

5. Indian childhood cirrhosis is discussed with reference to probable etiologic factors.

Congenital syphilis, kwashiorkor, and nutritional fibrosis do not appear to be related to this condition. Clinical and histologic data seem to indicate that Indian childhood cirrhosis is a form of chronic hepatitis, allied to chronic progressive hepatitis following viral hepatitis, culminating in cirrhosis.

This study has been carried out by grants from the Madras State Research Fund. We are grateful to the Director of Medical Services, Madras, and to the Secretary, Madras State Research Fund, for seconding one of us (V.B.R.) for work on this research and to the Director, Nutritional Research Laboratories, Coonoor, for so kindly permitting one of us (S.S.) to collaborate in this work on the pathologic aspects. Follow-up study of kwashiorkor has been supported by grants from the Indian Council of Medical Research.

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Xeroderma pigmentosum

A report on 6 cases in South African Bantu children

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XERODERMA pigmentosum, so called by Kaposi in 1870, is defined by Ormsby and Montgomery,[1] as "a rare disease, beginning in early childhood and characterised by hyperpigmentation, atrophic areas, telangiectases and warty and malignant growths. There is marked photophobia. Keratitis is common and nodules and opacities occur on the cornea, often obstructing vision to a marked degree."

During the past year we have been able to study 6 cases of this condition in the South African Bantu. This communication mentions the pertinent literature, provides a clinical report on the 6 cases, and the results of investigations carried out to determine the most effective therapy.

Apart from one other report dealing with 8 cases,[2] we believe this to be the largest series of cases of xeroderma pigmentosum reported to date.

The salient features of the disease are well described in most standard dermatologic textbooks.[1, 3, 4] Cases have been reported from most parts of the world, but authorities have agreed that it is especially rare among Africans.[5] Only 1 Negro woman and 7 Africans with the disease had been reported up to 1956.[5]

The first 3 Bantu patients, described by Loewenthal and Trowell in 1938,[6] were brothers. In 1940, King and Hamilton[7] described a 17-year-old Negro girl with the disease. Her parents were cousins. Cohen and colleagues[8] reported 1 case in a Bantu in 1952 but did not give full details. Targowsky and Loewenthal[5] mentioned 2 cases and described in detail a 6-year-old Msutu boy with the disease. Three Bantu cases were mentioned by Rose[9] in 1958, representing the total number of cases of xeroderma pigmentosum at Baragwanath Hospital in Johannesburg during the 10 year period.

CASE MATERIAL IN PRESENT STUDY

Case 1. Simon, a male Msutu child of 11 years.

History. At the age of 7 years the child developed photophobia. Black spots appeared on the face, then gradually spread over the body. Exposure to sunlight aggravated the condition.

Superficial ulceration of the lower lip had been present for 2 years. The patient was unable to attend school because of poor vision.

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Family history. The child is a descendant of Pusholi, a brother of Moshesh, former chief of the Basutos. It was the custom of royal descendants to intermarry "to keep the royal blood pure."

The family trees were obtained from the patient's grandmother, Deborah, and verified by the patient's father (Figs. 1, 2, and 3).

Physical examination. Darkly pigmented spots, varying in size from pinhead to 0.5 sq. cm., were seen on the face, neck, shoulders, and chest. There were very few lesions on the buttocks, thighs, inner aspects of the arms, and none on the scalp, soles, or palms. Depigmentation, less prominent, consisted of lesions of similar size over the face and shoulders.

The lower eyelashes were scanty and slit-lamp examination showed diffuse opacities in the corneal epithelium. On the surface of the conjunctivae brown patches formed a ring around the limbus. The irises were normal.

The lower lip showed superficial ulceration.

Case 2. A Msutu boy of 2½ years.

History. Small white spots commenced to appear on the face at 6 months of age. They gradually spread to the shoulders, body, arms, and legs and the spots on the face became black a few months before admission. A horny growth developed on the left cheek and detached spontaneously when he was 2 years old. His eyes watered when exposed to sunlight but his eyesight was normal.

Family history. There was no history of consanguinity between the parents. There are no siblings and no other family members are known to suffer from the illness.

Physical examination. Depigmented lesions, giving a "salt and pepper" appearance, were present over the body, excluding the scalp, buttocks, scrotum, palms, and soles. They were less marked on the insides of the thighs and upper arms. Darkly pigmented spots of 1 mm. to 0.5 cm. size were present over the face and neck. There was an atrophic area on the left cheek where the warty growth had become detached.

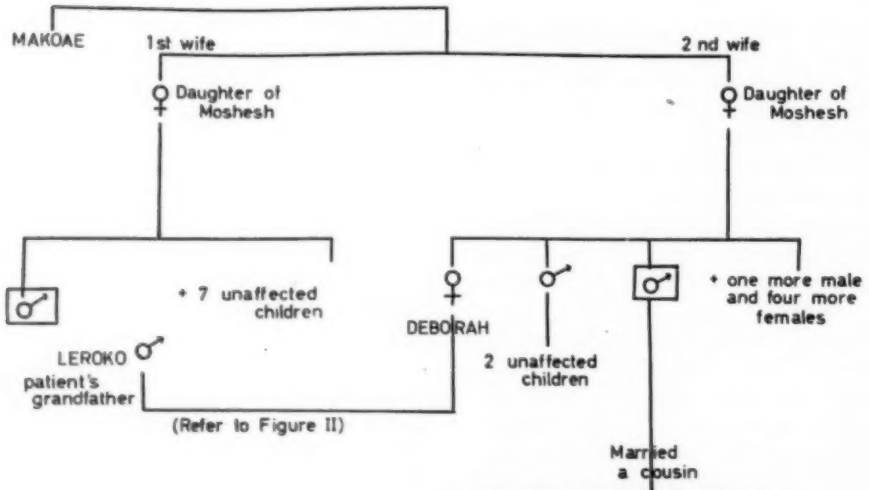

Fig. 1. Family tree of patient's grandmother, Deborah.

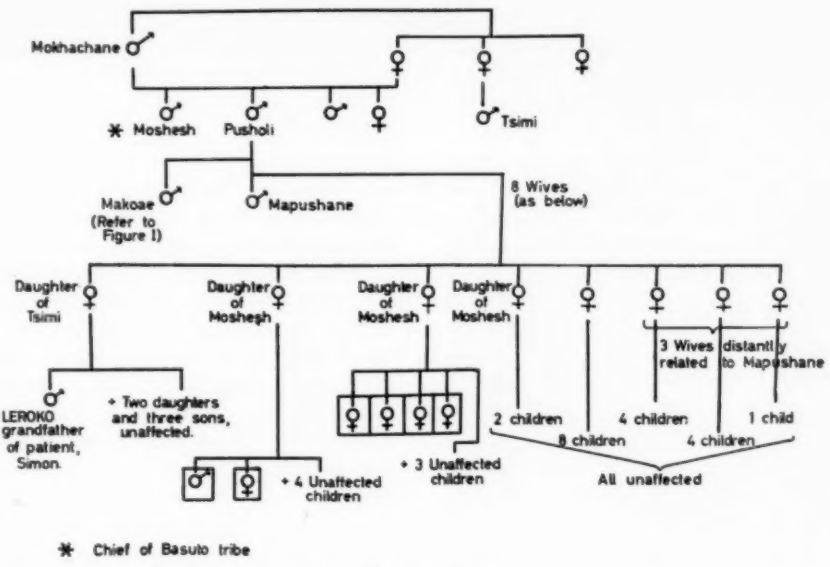

Fig. 2. Family history of patient's grandfather, Leroko.

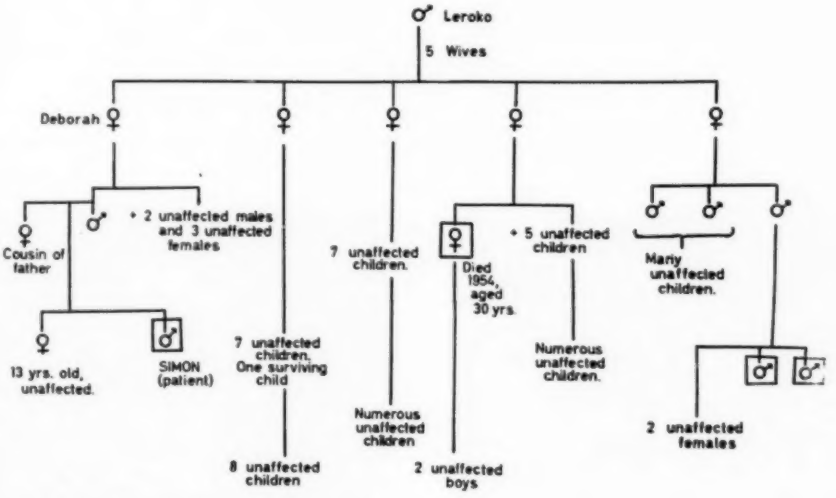

Fig. 3. Family tree of patient, Simon.

The lower eyelashes were scanty but the conjunctiva and cornea of both eyes appeared normal.

Case 3. A male Shuana child of 2½ years.

History. Since the age of 2 years there had been epiphora and redness of the eyes, especially after exposure to sunlight. At the same age white spots had developed on the face, becoming darker in color and spreading to the shoulders and chest. Sunlight aggravated the lesions and the lips were often sore.

Family history. The patient's mother and father were cousins. There were no known cases of the condition in the parents' families. An elder, similarly affected, brother is described below as our fourth case.

Physical examination. Areas of pigmentation and depigmentation were present on the face, neck, and shoulders. A small pigmented patch was present on the dorsal aspect of each forearm. Areas of depigmentation predominated and are well shown in Figs. 4 and 5.

The eyelids appeared normal but deeper areas of the conjunctiva appeared infiltrated. Vision was normal.

The lower lip showed ulceration and the upper lip was deformed, with depigmentation and scar tissue.

Case 4. An 8-year-old brother of the patient in Case 3.

History. Epiphora had been present since the age of 7 months and by 18 months of age white patches were visible on his eyes which were photosensitive. At the age of 2 years he developed black spots on the face, later on the neck, then over the whole body. After a year, lighter areas developed over the same distribution. The skin changes were worse during the summer.

Physical examination. Depigmentation, coalescent in places, predominated over pigmentation, and the lesions were seen on the face, neck, shoulders, the upper part of the thorax, and to a lesser extent on the dorsal surfaces of the forearms, with minimal involvement of the legs (Fig. 6). Atrophic areas were present over the left ear, the back, and forearms. On the scalp, small areas of pigmentation and depigmentation were present over the temporal, occipital, and frontal areas.

On the right side, there was pigmentation and depigmentation of the upper and lower eyelids. There was early band-shaped degeneration of the cornea, with clouding and opacity of the corneal lamellas and superficial corneal vascularization. On the left side there were central leukomas with ulcer formation. Photophobia was marked and vision amounted to little more than light perception.

Ulceration and atrophic areas of the lower lip were present.

Case 5. A 4-year-old male Bantu child

Fig. 4.

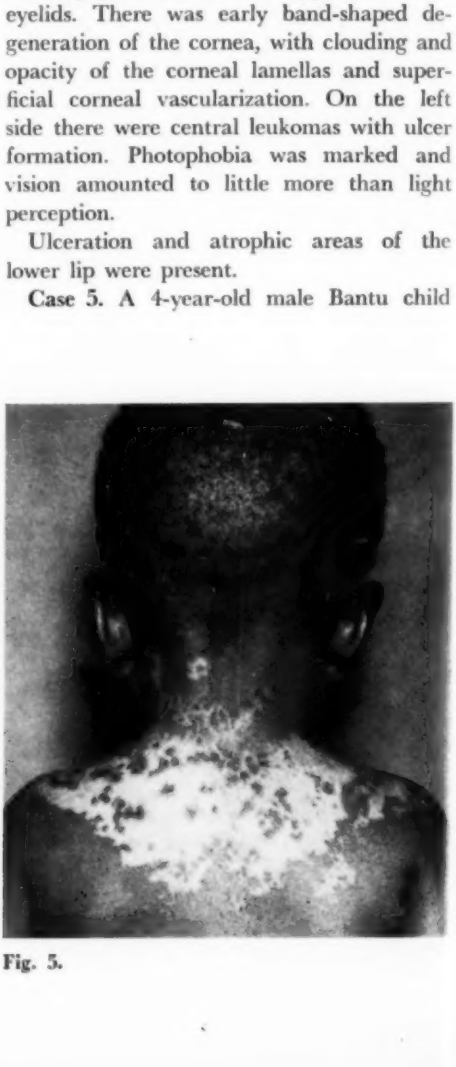

Fig. 5.

of unknown tribe. No history was obtainable.

Physical examination. The lesions were most marked over the upper half of the body. Darkly pigmented areas of up to 0.5 cm. diameter were present over the face. The neck, shoulders, upper part of the chest, back, arms, and abdomen showed progressively lighter areas of pigmentation, in that order. Depigmented areas of up to 0.25 cm. diameter were seen on the trunk and extremities.

Atrophic areas were seen on the face and especially above the upper lip. Heavily pigmented warty growths were scattered over the face and one was present on the right shoulder.

There were superficial ulcers and areas of leukoplakia of the upper and lower lips. Gross dental caries were present, with gingivitis. The distal part of the tongue was superficially ulcerated.

A black mass of about 4 cm. diameter, with elevated edges and central ulceration, was present on the scalp over the left frontal area, with an adjacent hard pink mass of 1 cm. diameter (Fig. 7). Large atrophic areas and warty growths were present over the vertex.

The scalp tumor was excised and a skin graft successfully applied. Histology of the tumor revealed a squamous carcinoma.

Since the skin graft, new warty growths have appeared on the scalp and he has developed a malignant tumor of the upper lip, which is growing rapidly.

The lower eyelashes were absent. Pigmentation and depigmentation were seen over the eyelids. Leukomas were present on the corneas and there was bilateral depigmentation round the limbi. Photophobia was very marked and the patient could only see objects a few inches away.

Case 6. A 3-year-old Bantu male of unknown tribe.

History. The child was admitted to the hospital for investigation of blindness. No further history is available.

Physical examination. Numerous pigmented and depigmented areas covered the upper part of the body. The lower lip showed superficial ulceration.

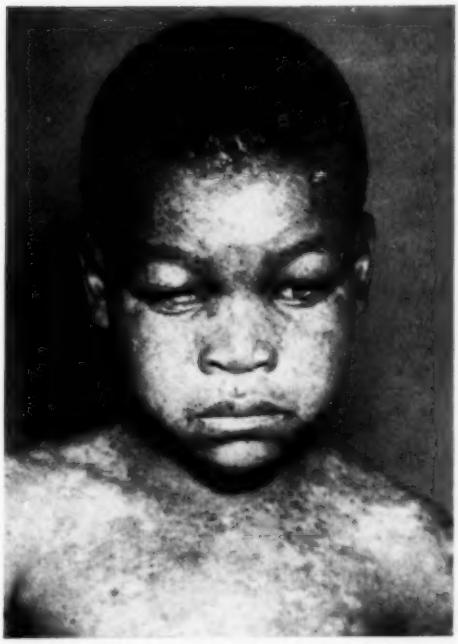

Fig. 6.

A pigmented spot at the limbus of the left eye detached spontaneously. Biopsy of a tumor of the tongue showed histologic features of an ulcerating, acutely inflamed, capillary angioma in which there were a few areas of plasma cell infiltration. There was no evidence of malignancy.

SKIN HISTOPATHOLOGY

Histologic examination of the skin was performed in 4 cases.

All showed moderate hyperkeratosis. Epidermal melanin pigment was increased and often extended as far as the stratum corneum. In the basal layer the pigmentation was patchy, areas of marked hyperpigmentation alternating with areas of hypopigmentation and sometimes depigmentation. Pigmentary incontinence was present in all but one case (Case 4). In all sections

Fig. 7.

there were alternating acanthosis and epidermal atrophy.

The dermis was mildly edematous and showed slight to moderate perivascular and subepidermal infiltration by lymphocytes and neutrophil leukocytes.

In one case (Case 5) a section from the scalp showed infiltration by a well-differentiated squamous carcinoma.

THERAPEUTIC TESTS

The upper parts of the posterior aspects of the thighs of 2 patients were each covered with cardboard, perforated with holes of about 2 cm. diameter. The exposed areas of skin were consecutively numbered and were uniformly covered with different ointments (Table II) in order to assess their protective values against ultraviolet light, to which each area was exposed. The reactions recorded are those produced by a fourth degree erythema dose to white people (exposure at 1 inch to a Kromayer lamp for 40 seconds). The results of these tests are shown in Table II.

In cases with severe pigmentary reactions there was preceding erythema, beginning about 4 hours after exposure and disappearing within 24 hours. In no case was primary pigmentation, that is, pigmentation occurring within 20 minutes of exposure, noted, though this type of reaction has been noted in the Bantu by Kooij and Scott.[10] The pigmentation was not clearly noticeable before 2 to 4 days had elapsed. Scaling occurred with severe pigmentary reactions.

DISCUSSION

The fact that at one time 6 patients with xeroderma pigmentosum were being investigated in our wards suggests that though the disease is distinctly uncommon among the Bantu, it is probably not as rare as was believed. The 6 cases described here bring to 16 the number reported in Africans, excluding that of 1 American Negro woman though not all cases have been fully described in the literature.

Macklin[11] maintains that the disease is conveyed by incomplete, sex-linked, recessive inheritance. The importance of consanguinity in the etiology of our cases is emphasized by the family trees in Figs. 1, 2, and 3. The polygamous customs of the Bantu portray this feature in a way which could hardly occur among white people. Attempts by the Bantu to "keep the royal blood pure" appear to have perpetuated the condition among their royalty. The family tree has been traced back further than Moshesh, a Bantu chief (approximately 1786 to 1870).

Though most descriptions of xeroderma pigmentosum appear in dermatologic journals, it should be noted that the patients in Cases 4 and 5 are almost blind. The child in Case 1 is unable to attend a normal school because of poor vision. It is therefore interesting to review briefly the eye changes which may occur in the disease, as described by Duke-Elder[12]:

"The eyelids are frequently affected and

are often the first area of the skin to show changes. In the milder cases, apart from an unusual tendency to form freckles and sunburn, no untoward event may occur until adolescence or early life, when multiple tumors, papillomatous and eventually carcinomatous and frequently pigmented, begin to appear; the first tumor may become evident in the eye. In the typical severe case, on the first exposure to sunlight in early life, an acute erythema develops, followed by a diffuse pigmentation resembling numerous gigantic freckles. This stage is followed by atrophy affecting particularly the lower lid, which becomes denuded of cilia, suffers entropion or ectropion and eventually may entirely disappear, resulting in the development of an exposure keratitis and secondary corneal ulcers."

The clinical features of our cases are

Table I. Results of laboratory investigations performed on 5 patients

	Case 1	*Case 2*	*Case 3*	*Case 4*	*Case 5*
Hemoglobin (Gm. %)	10.8	11.9	11.4	12.7	13.5
Leukocytes (per c.mm.)	5,100	7,000	7,000	6,000	18,000
Polymorphonuclear leukocytes (%)	45	32	54	24	22
Lymphocytes (%)	49	66	40	74	74
Sedimentation rate (mm. in 1 hour Westergren)	7	3	20	11	—
Total serum proteins (Gm. per 100 ml.)	8.2	7.0	8.0	8.2	7.0
Albumin (per cent)	50.1	52.7	54.3	50.4	47.0
α_1 (per cent)	5.0	5.4	3.2	5.9	5.0
α_2 (per cent)	12.9	10.8	11.9	11.9	13.1
β (per cent)	11.0	13.9	10.6	11.6	10.7
γ (per cent)	21.0	17.2	20.0	20.2	24.2
Mucoproteins (mg. per 100 ml.) (normal 40 to 130)	36	97	48	48	72
Transaminase: serum glutamic pyruvic transaminase (Cabaud units) (normal 4 to 40 units)	4	7	5	4	11
Serum vitamin A (I.U.) (normal 60 to 200)	45	96	96	115	23
Ceruloplasmin (mg. per 100 ml.) (normal 16 to 33)	23	27	24	21	21
Copper (gamma per 100 ml.) (normal 99 to 188)	172	201	161	190	181
Thymol flocculation (units)	0	0	2	0	0
Colloidal gold	0	0	0	0	0
Zinc sulfate	7	8	10	12	8
Bilirubin	Normal	Normal	Normal	Normal	Normal
Urinary porphyrins	No excess	No excess	—	No excess	No excess
[a]Amino nitrogen-urine (normal in 18 cases 2 to 35 mg. per 100 ml.)	135.4	14.9	154 48.5	18.7	37.4 124.2
Amino acid-urine	No excess	No excess	Excess of glycine, glutamine, alanine, and cysteic acid	No excess	Excess of glycine, alanine, glutamine, serine, cysteic acid, and threonine
Amino acid-blood (normal 4 to 7 mg. per 100 ml.)	—	—	4.5	—	5.4
Kollmer and Price tests	Negative	Negative	Negative	Negative	Negative

generally similar to those described in other communications. An unusual feature, however, is the large area of depigmentation of the skin seen in brothers in Cases 3 and 4 (Figs. 4, 5, and 6). Telangiectases, though described as a characteristic feature of the disease, were seen in only 1 of our patients in whom a biopsy of a tumor of the tongue showed an acutely inflamed capillary angioma. It is possible that angiomas are hidden by the skin pigment. As typified by our cases, the disease predominantly affects exposed parts of the body but tumors may also occur in the mouth and more especially on the tongue.

Reference to Table I shows that, of investigations done to try and throw further light on the etiology of the disease, 2 are sufficiently interesting to merit discussion. It has been reported by Gianotti[13] that serum vitamin A values may be very low in this disease. Only Case 4 out of 5 cases investigated by us had a normal serum vitamin A level, the rest being low. However, control studies of vitamin A in 5 Bantu children convalescing from other conditions revealed values of 111, 111, 93, 81, and 48 I.U. The Bantu suffer from various degrees of malnutrition and in view of low values in control cases, the findings in our cases are not regarded as significant.

In 2 of our cases an excessive amino-acid excretion was found in the urine by chromatographic studies. High α-amino nitrogen excretion in the urine was in keeping with these findings, the significance of which is uncertain. The patients were not suffering from kwashiorkor, which is common in the Bantu and which may cause an increased excretion of isoleucine and a higher excretion of phenylalanine than tyrosine.[14] Renal tubular leakage is a possible explanation since blood α-amino nitrogen values were normal, thus excluding high blood values as a cause. Renal studies were not performed in our cases.

Table II. Protective values of local ointments to ultraviolet light in Cases 1 and 4* before and after oral administration of dexamethasone and chloroquine phosphate

	Metiderm†	*Nivea cream*	*Vaseline brand Lip Ice*‡	*Placebo*§	*Control*
Case 1					
Without oral medication	++	+++	½+	++	+++
After dexamethasone	++	++	–	–	++
After chloroquine phosphate	–	–	–	–	–
Case 4					
Without oral medication	+	++	½+	++	+++
After dexamethasone	+	+	–	–	+
After chloroquine phosphate	++	++	–	++	++

– No reaction.

+ Mild pigmentation.

++ Moderate pigmentation.

+++ Severe pigmentation.

*The above tests were also carried out on patient in Case 5. Owing to his darkly pigmented skin no reactions were visible.

†The Metiderm formula is:

Ingredient	*Percentage by weight*
Prednisolone	0.50
Zinc stearate	6.00
Polyethylene glycol 1,500	42.50
Polyethylene glycol 6,500	12.00
Propylene glycol	35.00
Distilled water	4.00

‡See discussion for constituents of Vaseline brand Lip Ice.

§The placebo is as above but without prednisolone.

The results of our therapeutic tests are shown in Table II. The following conclusions may be drawn. Of the local preparations we used, the best protection was provided by a proprietary ointment* containing the following ingredients: white petroleum jelly, paraffin wax, white ozokerite wax, silicone oil 555, homomenthyl salicylate, white beeswax, camphor, carnauba wax, ungerer bouquet, and hexachlorophene. This ointment was of value in Case 1 in healing and protecting the lower lip, which was the site of diffuse superficial ulceration.

Dexamethasone gave slight protection to the skin when given orally.

The results of oral administration of chloroquine phosphate were inconclusive and we considered the possibility of a technical error. We were unfortunately not able to repeat the test. In this connection Colomb[15] described 2 cases in Moorish children with xeroderma pigmentosum. On administration of chloroquine sulfate there was a definite clinical improvement in spite of certain exposure to sun. When the drug was stopped relapses occurred and when it was restarted there was again improvement of photophobia and flattening of skin excrescences as before. It appears therefore, that this drug warrants further clinical trial.

Smithers and Wood[16] found by means of experiments similar to ours that the best local skin protection was given by the following ointments, which were not available to us for comparison:

Cream	
Titanium dioxide	25%
Magnesium stearate	12.5%
Butyl stearate	12.5%
Menthyl salicylate	20.0%
Pigment base	2.0%
Vanishing cream	28.0%

Pigment base	
Burnt umber	50%
Red ferric oxide	25%
Yellow ferric oxide	25%

*Vaseline brand Lip Ice, manufactured by Chesebrough-Pond's International, Ltd., P.O. Box 9724, Johannesburg.

Vanishing cream	
Stearic acid	15%
Cetyl alcohol	1%
Triethanolamine	1.5%
Diethyleneglycol monoethylether	10%
Distilled water	72.5%

We have prescribed sunglasses for all our patients in order to protect their eyes against ultraviolet light.

SUMMARY

Xeroderma pigmentosum is a rare disease regarded as especially uncommon in Africans. Six cases are described in Bantu children, bringing the total number of reported cases in Africans, excluding 1 case in an American Negro woman, to 16.

The condition, according to Macklin, is conveyed by incomplete sex-linked recessive inheritance. There is a strong history of consanguinity in 1 of our cases, dating back to the middle of the last century.

The clinical features are described. An angioma, regarded as a common feature, was seen in only 1 case. Depigmentation predominated markedly over pigmentation in 2 brothers.

Amino-aciduria was found in 2 patients. The significance of this finding is uncertain.

Tests with exposure to ultraviolet light were carried out to assess the protection provided by dexamethasone and chloroquine phosphate by mouth and various ointments locally. Dexamethasone gave slight protection but the tests evaluating chloroquine were inconclusive. According to the literature oral chloroquine may give good palliative results. An ointment containing silicone, oil, homomenthyl salicylate, and hexachlorophene, among other ingredients, gave the best local protection.

The eye lesions were severe in 3 cases. Dark eyeglasses should be used for protection against ultraviolet light.

It is a pleasure to acknowledge the encouragement and interest in this work shown by Prof. J. G. Davel. These cases are published with the consent of the acting superintendent of Pretoria General Hospital, Dr. J. Vorster. Dr. I. W.

Simpson of the Department of Pathology kindly caried out the histologic examinations. We wish to thank Mr. T. Marais for the photographs. Dr. G. H. Findlay supplied stimulating criticisms of the work and manuscript. Dr. L. de Villiers carried out the majority of the chemical studies, drew the family trees, and gave valuable advice. The copper and ceruloplasmin estimations were done by Dr. J. J. Theron of the C.S.I.R. Dr. J. S. Maree helped in the clinical study of some of the earliest cases. Dr. J. Marshall also gave valuable advice regarding the manuscript and literature.

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MEDICAL PROGRESS

Diarrhea in children: a historical review

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DIARRHEA, or dysentery, is one of the oldest diseases known to mankind, and references to this uncomfortable and dangerous condition are found in the most ancient writings of antiquity. As a matter of fact the modern word "cholera" derives from the Hebrew *choli-ra,* and in the Biblical writings of the ancient Palestinians we meet the first recorded references to this disease. In II Chronicles XXI, 19, it is recorded that Jehoram died of an incurable flux lasting two years. A later scribe, in Acts XXVIII, 8, described not only the intractable diarrhea besetting the father of Publius, but also recorded the first psychiatric approach to the treatment of the problem when Paul cured the venerable patient with the laying on of hands.

In the Greek period, Hippocrates had a great deal to say about diarrhea, although he wrote no special text on diseases of children.

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He noticed even the influence of weather: "For when suffocating heat sets in all of a sudden, while the earth is moistened by vernal showers . . . men's bellies are not in an orderly state, for it is impossible, after such a spring, but that the body and its flesh must be loaded with humors. . . . Dysenteries are also likely to occur. . . . "[1] Hippocrates seems also to have been aware of different types of this illness: Diarrhea, "when they are set with fever" or "with inflammation of the liver," or "such as are painful" had a bad prognosis. Cases "attended with blood and scrapings of the bowels" (bacillary dysentery?) enjoyed a milder prognosis.[1] Hippocrates was one of the first to blame diarrhea on teething.[1] He noted the importance of anuria in diarrhea: "those who pass from below humors and scarcely urinate . . . are sickly."[1] He was also aware of chronic diarrhea (celiac disease?): "They that pass not water in proportion, but from their belly from earliest childhood passes constantly undigested material, are sickly."[1]

In the third and fourth centuries immediately following the birth of Christ and the beginning of the disintegration of the Roman

Empire, very little was written on either medicine or diarrhea. Of this period we have only the writings of the Talmudists, and the excellent textbook on pediatrics by Soranus.

The Talmudists, who in their voluminous discussions and annotations left us a detailed panorama of life in the early centuries of our era, stressed that sudden changes in living habits, particularly overeating, were apt to cause diarrhea. Rabbi Samuel stressed the importance of fluids: "He who eats without drinking, eats blood from his own body . . . and this is the beginning of diarrhea."[2] There is no question that diarrhea or dysentery was considered a severe illness. Rabbi Jose wished to die of this disease, for the suffering associated with it was so great that it would absolve its victim from the tortures of hell in the afterworld.[2]

Their therapy may seem very hazardous to us today, but as we shall see, the treatment recorded by the Talmudic scholars remained essentially unchanged for over a thousand years. They advised external applications to the abdomen—usually heat of some sort, or irritants such as wine and oil.[2] There was also a form of cupping to the navel.[2] In the diet, they advised old apple, or grape wine, or lemons. For tenesmus, the daughter of Rabbi Asche was given pepper seeds in wine. Plenty of water was also advised.[3]

It is possible that the rabbis were aware of the contagiousness of dysentery. While it was a holy duty to visit the sick, they advised against visiting patients with diarrhea and eye diseases.[4] And despite the deep-seated rabbinical objection to tampering with the bodies of the deceased, these ancient worthies advised fumigation for the corpses of victims of diarrhea.[5]

During this same period, the first known treatise especially devoted to pediatrics was written. Soranus of Ephesus (98-117) wrote this book consisting of 23 chapter headings, amongst them, "On flux of the Belly." Soranus is the first author to mention the famous fingernail test for purity of milk. This test continued in use for over 1,600 years, and was repeated almost verbatim in the first English book on diseases of children, written by Thomas Phaer in 1545: "That mylke is goode that is whyte and sweete; and when ye droppe it on your nayle and do move your finger, neyther fleteth abrod at every stiring nor will hange faste upon your nayle, when ye turn it downeward, but that whyche is betwene bothe is best."[6] This ancient test for the palatability of milk is repeated even as late as 1752 in W. Smellie's *Treatise on the Theory and Practice of Midwifery.*[7]

The disintegration of the Roman Empire was followed by the dark ages, unenlightened for medicine as well as it was for other sciences and arts. Medical writing was confined chiefly to the Arabian physicians who devoted themselves to translating the ancient Greeks. The translations were later reintroduced into Europe by Hebrew authors who retranslated the Arabians into Latin. One of the best known manuscripts on pediatrics of this period is *Liber de Passionibus Puerorum Galeni* attributed to Galen but really a compendium of many classic medical essays gathered together during the sixth to the ninth centuries. Nothing new was added to the treatment of diarrhea in this book.

However, Rhazes (852-932), a Persian of a somewhat later period, in referring to diarrhea, bridged the ancient with the most modern, by attributing the disease to teething, to catching cold (parenteral infection) and to spoiled milk.[6] Rhazes was a busy physician who treated and wrote about many diseases, and he found the incidence of diarrhea high. A compatriot of Rhazes, Avicenna, or Ibn Sina, also had a chapter on children's diseases and included therein a paragraph which attributed diarrhea to teething, reaffirmed the need for belly fermentations and fruit seeds, but added two new ideas. The first was the advice to, ". . . drink five grains of kids rennet in cold water. . . ." The administration of glandular organ was repeated in succeeding literature on the subject until the modern era, and forms an interesting background to our contemporary use of pancreatic extracts in chronic diarrhea. The other admonition was,

". . . instead of milk let him take . . . some barley soaked in water."[6] The prohibition of milk and the use of barley water bring us right up to the present.

The Renaissance with its awakening of scientific thought produced many writers on medical subjects, and the discovery of the art of printing facilitated the survival of much of their work. The first printed book on pediatrics appeared in 1472. It was written by Paulus Bogellardus (Fiume, Italy, ?-1492) and first appeared in Padua. Diarrhea fills a long chapter, and the author frankly refers back to Galen, Avicenna, and Rhazes. A significant contribution, however, was his thought that some cases of diarrhea clear up when the baby is fed goat's milk diluted with cool water.[7]

The second printed book on pediatrics by Bartholemus Metlinger (Augsberg, ?-1491) appeared in 1473. Metlinger also gives the etiology of dysentery as teething, but his treatment is good: "If the child is not nursing, give it skimmed goat's milk, also almond milk diluted with heated water."[7] This book of Metlinger had a tremendous influence on pediatrics, for it was incorporated by Rosalin into a book on midwifery, and translated into English, enjoying numerous editions in both French and English.[7]

The possibility of seeing oneself in print apparently was stimulating to pediatricians then as now, for those early years soon saw two additional treatises on the care of children. One author, Cornelius Roelans, wrote his *Diseases of Children Still in the Cradle,* toward the end of the fifteenth century, and the second, Sebastian Oestreicher, published in 1546 what was really an abstract of Roelans. Roelans' work is in turn a compilation of the classic authors. In his methodical list of 52 childhood diseases he included diarrhea, but neither he nor Oestreicher had more to add than has already been noted.

The "father" of pediatrics in England, Thomas Phaer, earned his title by writing *The Boke of Children* in 1584. The book was still another compilation of the classic authors and its chief importance is historical, since its existence illustrates the Renaissance tendency to translate the classic authors into the vernacular. His ideas of the etiology of diarrhea were not new. His treatment was also not new although it is interesting that he stressed abstention from milk for two hour periods during the disease and then advised heating it when its use was resumed.[7] Neither Robert Penell[8] nor Franciscus Sylvius[9] (Amsterdam, 1674) (Sylvan fissure and aqueduct) added anything new to the subject.

In France, Simon de Vallembert was the first, in 1565, to publish a treatise on pediatrics, *Cinq livres de la manière de nourrier et gouvener les infants des leur naissance.* This author added nothing new, but his classification of the different forms of the illness is interesting: "1, food is passed much as when eaten (The Greek, lientery); 2, skinning of the intestines (The Greek, dysentery); and 3, neither of these two (called diarrhea by the Greeks)."[7]

Walter Harris in his *De Morbis Acutus Infantum,* published in London in 1689 and for a hundred years the most popular English book on pediatrics, was the first to strike an original and surprisingly modern note on the subject of diarrhea: "Of all the Causes of Diseases of Infants, which have been already mentioned, and all that may be derived from them, center in one next and immediate Cause, namely an acid prevailing universally." His use of the word acid is not fortuitous, for after citing diarrhea as the usual cause of acidosis, he goes on to give a description of the acidotic state which clearly indicates that he saw and studied cases of intestinal intoxication: "If the Affair is further prolonged, they grow paler and paler . . . the countenance. . . . A Mixture of yellow or green . . . the stomach swells . . . a pimple or two on the skin. . . . He wheezes also, and draws his Breath so hard . . . they sometimes produce Gripings, sometimes greenish stools, and sometimes violent Looseness. . . ."[7] Harris, like Hippocrates, also stressed the seasonal appearance of diarrhea: "From the middle of July to about the Middle of September, the Epidemical Gripes of Children are so ripe every Year, that more of them usually

die in one Month than in three or four of any other Time; for the Heat of that Season commonly Weakens them. . . .[7] In his treatment he actually attempts to neutralize the acid by the use of "testaceous powders or absorbents of acid" and he gives a long list of alkaline-producing substances.[7]

The Herberdens, father and son, in their book, *An Epitome of the Diseases Incident to Children* (London, 1807), included a small chapter on diarrhea which also advised chalk medication in addition to astringents, and sometimes both an emetic and a mild cathartic like rhubarb.[7]

One of the most famous essays on diarrhea is that by Benjamin Rush. Written in 1777, it is a concise, careful, and complete description of cholera infantum.[10] He compared the summer diarrhea of infants with a disease of adults which he called, "cholera and remitting fever." Since true or Asiatic cholera did not strike in this country until the epidemic of 1832-1833, he was probably identifying the bacillary dysentery of infants with bacillary infection in adults. The same identification was made on a bacteriologic basis in 1901-1903 by the Rockefeller group within four years after Shiga had established the etiology of adult dysentery.

In his essay Rush emphatically denied the ancient idea that dentition or worms caused diarrhea. He stressed the factor of warm weather, and while he was by no means original in that, he did, contrary to the statements of Rhurah, make an innovation as to prophylaxis. He was the first to suggest the benefits of sending young infants to the country for the summer months. Additional suggestions for prophylaxis (he was unique in stressing this aspect of the disease) included the use of daily cold baths, attention to suitable summer clothes, eating of salted meats, inhibition of sound old wines, and personal cleanliness. His treatment was not original: emetics, cathartics, clysters, laudanum, diluting drinks, plasters of treacle to the abdominal wall, and warm sitz baths. The great contribution of Rush was his emphasis on the relationship of summer heat to diarrhea, and the importance of proper hygiene in the prevention of this illness.

In the early part of the nineteenth century there appeared the first descriptions of the postmortem changes following diarrhea. James Jackson was the first actually to study the tissue changes.[11] Besides the general emaciation, he found evidence of inflammation in the stomach and duodenum. There was usually also mucosal inflammation in the rest of the small intestine. In the large bowel he occasionally found not only inflammation, but ulcers "resembling the canker spots in the mouth." A cursory description of the pathology of cholera infantum was later included in a book on the treatment of children by William P. Dewees in 1825.[12] This book, incidentally, gives the first suggestion we have been able to find for the parenteral injection of salt and water in this disease. The first exclusively pathologic report on diarrhea was made by W. E. Horner. His report first pointed out that cholera infantum produced a follicular disease affecting the mucous glands and follicles, rather than a common vascular type of inflammation.[13] These pathologic findings were confirmed in 1858 by J. Lewis Smith.[14]

Some of the articles written about diarrhea during the eighteenth and nineteenth centuries were confusing and bizarre. They often followed not only the ideas but even the language of the middle ages. As late as 1837 the "miasmic" theory of the causation of diarrhea appeared in print.[15] There was an attempt to tie together 3 diseases in a pamphlet entitled, "An attempt to Establish the Original Sameness of Three Phenomenum of Fever . . . described by Medical writers under the Several Names of Hydrocephalus Internus, Cyanche Trachealis and Diarrhea Infantum."[16] Another article reported a case of diarrhea treated with nitric acid.[17] One paper purported to prove that cholera infantum was the same disease as Asiatic cholera and that both could be prevented and cured by the same measures as were then used against scurvy,[18] while another publication found diarrhea to be caused by the malaria of crowded places, as in cities,[19]

There were also many articles which, though adding nothing new, tabulated and classified the many manifestations of the disease, and summarized its treatment.[20] However, a new basic science was destined to be born before further real progress could be made.

Toward the end of the nineteenth century, the genius of the new science of bacteriology was brought to bear on the subject of cholera infantum. Escherich in Germany and Booker in this country[21] had long suspected a bacteriologic basis for this disease. The chief obstacle to the isolation of a specific organism and its identification as the specific cause of diarrhea was the plethora of organisms normally found in the intestinal tract. Escherich in 1886 first established the *Bacillus coli* as the chief inhabitant of the lower bowel, and *B. aerogenes* as the principal inhabitant of the upper intestinal tract.[22] The number of intestinal bacterial inhabitants was quickly increased by Gessner[23] in 1889, who isolated 7 additional organisms from the duodenum alone, and by Gillespi,[24] who in 1893 reported 24 different organisms from the stomach. These investigators were followed by a host of others who in the cadaver and by means of observations on patients with fistulas isolated a constantly increasing number of such organisms: Gilbert and Lion,[25] 1893; Dallemagne,[26] 1894; Macfayden, Nencki, and Sieber,[27] 1891; Ciechomski and Jakowski,[28] 1894; Gartner,[29] 1889; Petruschky,[30] 1896; Smith,[31] 1895; Welch,[32] 1900; and Durham,[33] 1900.

Since Pfeiffer's discovery of the specific lysis of organisms by serum from convalescent patients had been adapted to the phenomenon of agglutination by Widal, and since the phenomenon of agglutination had been applied successfully by him in the diagnosis of typhoid fever, a method applicable to the problem of diarrhea seemed at hand. Shiga[34] was soon able to show that, in dysentery, the incriminated organism was precipitated by the convalescent serum of a patient recovering from the disease. This method also proved successful with children in the work of Duval and Bassett[35] during the summer of 1902. In addition, Gay[36] showed that the serum of horses immunized with Shiga's bacillus could be used in identifying suspicious organisms. These methods, in addition to general cultural and sugar-reducing studies, and an exhaustive consideration of the conditions of its occurrence in children ill with diarrhea in different localities, became the underlying principles in a series of new investigations undertaken at the instigation of the Rockefeller Institute for Medical Research.[37]

Simon Flexner, under whom the study was organized, established a centrally motivated but geographically widespread investigation into the general relationship of the dysentery bacillus and the summer diarrhea of infants and children. The organizational problems of central control and individual responsibility foreshadowed similar projects, on a gigantic scale, in the scientific investigation carried on during World War II. There were 18 hospitals and nurseries, and 22 investigators involved in this study. The report is a classic in its field. At the conclusion of the study it could be stated with reasonable assurance that the *Bacillus dysenteriae* was isolated in considerable numbers from the intestinal discharges, particularly in the mucus, of children suffering from summer diarrhea. The close association of this bacillus with the intestinal mucosa as found on the autopsy material by John Howland which is the established pathogenic action of the bacillus for human beings, and the fact that the blood of children convalescing from this disease agglutinated the organism, all strongly supported the presumption of a causal relationship between the organism and the intestinal lesions.

The bacteriologic and pathologic studies were reinforced by concomitant clinical studies; from these, certain facts were drawn which had a direct bearing on control of the disease. All observers agreed that the disease was one of poor hygienic environment, warm weather, and artificial feeding. Dirt, heat, a known bacillus, and cow's milk, all seemed to point an accusing finger at the methods of preparing artificial formulas. Since the

treatment with dysentery antiserum was shown to be of dubious benefit even in these earliest studies, the best practical value of utilizing the new knowledge concerning the etiological factors was in the prevention of the disease.

The importance of dirt and warmth in rendering milk lethal had been anticipated by the studies of Park and Holt[38] during the summers of 1901 and 1902. The philanthropist Straus, convinced by Park that the impure milk fed to New York's infants was responsible for the tremendous incidence of diarrhea, established a series of milk stations at which pasteurized milk was either given away or sold at nominal prices. Results were compared when children were fed this milk, also a *good* bottled milk, and also *best* bottled milk, and the notorious store milk delivered and kept in large cans at store temperatures. The results are so concisely expressed in the original tables, that we reproduce them here.

The striking difference between the effects of summer and winter on the outcome of feeding with differently treated and stored milks pointed in one direction: heat promotes multiplication of bacteria in milk, and heavily contaminated milk results in disease. Not only Park but men like Jacobi, Kerley, and Holt were quick to realize the clear indication resulting from this study: mandatory milk pasteurization.

Implementation of the conclusions drawn from these studies resulted in a tremendous saving of human life. This may be illustrated by a few statistics. In the City of New York, during the year 1900, there were for each 1,000 living births, a total of 140 deaths from diarrhea under the age of 1 year; corresponding figure for 1930 was 55. In 1889, 31 per cent of all deaths in babies under 1 year of age was caused by diarrhea; in 1929 the figure was 10 per cent. The improvement in infant mortality was of course, not confined to New York City, nor indeed to the United States. Variot in Paris, chief of the Belleville Baby's Hospital, realized the need

Table I. Food and results—winter

	Did well	*Did fairly*	*Did badly*	*Died*	*Totals*
Store milk	47	6	2	0	55
Condensed milk	39	5	2	2	48
Good bottled milk	51	13	1	3	68
Milk from central distributing stations	35	20	4	0	59
Best bottled milk	5	0	1	0	6
Breast feeding	7	1	0	1	9
Totals, excluding cases counted twice	156	41	8	6	211

Table II. Food and results—summer

	Did well	*Did fairly*	*Did badly*	*Died*	*Totals*
Store milk	21	23	20	15	79
Condensed milk	22	20	14	14	70
Good bottled milk	37	23	29	9	98
Milk from central distributing stations	84	33	24	4	145
Best bottled milk	9	3	0	0	12
Breast feeding	17	7	7	0	31
Totals, excluding cases counted twice	184	108	88	41	421

for clean milk and fed his charges pasteurized milk in sterilized bottles. When 2 years later, Dr. Dufours[39] of Fecamp followed his lead, he succeeded in reducing the mortality from infant diarrhea from 76.6 to 2.8 per cent.

The new bacteriologic studies had also the effect of resolving an ancient debate. From the earliest times, as we have seen, numerous authors had suspected the role of hot weather in producing diarrhea. Hippocrates[40] saw in it an influence on body humors. Howell[41] believed that the summer heat exhausted the tone of the skin and forced an undue amount of blood into the visceral organs, causing abdominal congestion and diarrhea. John Chapman[42] of London thought the role of heat was to produce a hyperemia of the spinal nerves which in turn disturbed the circulation of the abdominal contents. Leonard Chalmer,[43] an American, thought that hot weather caused diarrhea in children because the heat exhausted them more quickly than it did adults, and that the digestive system was disturbed by this exhaustion. Iloway[44] believed that heat worked its effect by inhibiting the formation of hydrochloric acid in the stomach, and that the diarrhea resulted from the absence of this ingredient in the digestive juices. It was Cooke[45] in 1828 who sugested that, while heat played a role, it was not the sole cause. In 1890, Rotch developed this thought to the point where he stated that heat affected the milk in such a way as to make its ingestion result in diarrhea. Rotch, incidentally, rode his hobby hard. He organized the first seashore home for city children as far back as 1887 (at Winthrop, Massachusetts) and there all milk served to the inmates was previously treated in an Arnold sterilizer. His efforts led to the organization of the famous Floating Hospital in 1894. With Mr. Walker, he established the Walker-Gordon farm in New Jersey. In 1892 he helped organize the first medical milk commission which resulted in the formation of the Association of American Milk Commissions in 1905.[46] While the identification of these specific organisms delineated a fairly specific group of patients with diarrhea, clinicians and bacteriologists were not long in finding, as we shall see, that they had by no means discovered the cause of all or even a majority of cases with this symptom.

The clinical and bacteriologic studies of the nineteenth century were roughly contemporaneous with a number of studies which laid the ground work for an understanding of the basic chemical and physiologic changes associated with diarrhea. Schmidt[47] in 1885 was the first to study the chemical changes in the body resulting from diarrhea. This work, performed on adults suffering from Asiatic cholera, and based on previous studies of the blood of normal subjects, demonstrated that acidosis was usually a concomitant of severe diarrhea. The first experiments leading to an understanding of acidosis had been performed by Walter in 1877.[48] He fed rabbits dilute hydrochloric acid, and found that the carbon dioxide content of the blood was inversely proportional to the amount of acid given the rabbits. He noted also that the rabbits exhibited a marked hyperpnea before death. In 1883 Stadelmann first noted that the dyspnea observed by Walter in his rabbits greatly resembled that found in diabetic coma and suggested that acidosis was the metabolic disturbance in the latter disease.[49]

The concept of acidosis enlarged rapidly. Following the lead of Stadelmann, the actual organic acids produced in diabetes and responsible for the acidosis were identified by Minkowski[50] and Magnus-Levy.[51] Maunyn considered acidosis as due entirely to the manufacture of an excessive amount of acids: acetone, diacetic acid, etc., as shown by their appearance in the urine.

Michaelis, a rare genius, both physician and physical chemist, brought his knowledge of chemistry and mathematics to the problem.[52] He established the existence of a constant pH in the body, and showed that one of the basic properties of human tissue is its ability to maintain an almost constant state in regard to its concentration of acid and basic ions. The symbol pH (the negative exponent [power] to the base 10 of the H ion concentration) was introduced by Sorenson

in 1909 as a suitable and convenient expression of the hydrogen-ion concentrations. The relation of these ions to each other scarcely varied even in pathologic states. By a study of oxidation and reduction systems in the body, and by combining this with his knowledge of buffers and their functions, Michaelis established the basic facts concerning chemical relationships which go into the maintenance of normal blood pH.

Lawrence J. Henderson, the talented chemist who became professor of biological chemistry at Harvard, digested these findings of Michaelis, added some of his own and some reported by Hasselbach and Gammeltoft.[53] He then elaborated the first, and to this date the most inclusive, formulation of the complex system of buffers by which the body fluids are maintained at the almost fixed pH of 7.4. This remarkable genius described the theory of neutrality regulation in the animal organism in 1908.[54] There followed a critical study of acid excretion in 1911.[55] Henderson studied the variations in urinary acidity in 1912 and 1913[56] and the acidosis in terminal-chronic nephritis in 1927.[57] During these same years there also appeared a number of summarizing articles and monographs in which he discussed facts and probabilities in relation to the basic properties of protoplasm.[58] In 1920 Henderson predicated that the body acidity depended largely on the relationship or ratio between blood bicarbonate and carbonic acid.[59] This relationship could be disturbed by a large number of factors, and, contrariwise, this relationship was protected by a great number of buffer solutions. These thoughts he summarized in a formula which he deduced from the mass action law which Arrheneus had used to describe the action of weak acids. Henderson's formula was experimentally confirmed by Hasselbach and the modified formula, now designated by both names, expresses the basic fact in the complexities of the situation: $pH = pK_1 + \log \frac{(BHCO_3)}{(H_2CO_3)}$.*

*Where pH has its usual significance (previously described) and pK is the connected dissociation constant of the acid (carbonic, phosphoric, protein acid, etc.).

Sellards was one of the first to elaborate a method by which acidity of the body tissues could be measured.[60] Henderson had already noted that such was the efficiency of the body's system of balances that the pH of the urine rarely varied more than a minute degree. Sellards set about to measure the amount of sodium bicarbonate that a subject could ingest before the urine pH changed. He found that in subjects where the bicarbonate content of the blood was normal, a relatively small amount of bicarbonate (1 to 2 Gm.) would change the normally acid urine to the alkaline side. However, if the plasma bicarbonate had been depleted (i.e., in acidosis), ten times that amount might be needed to effect the same change. This simple finding Sellards placed on a quantitative basis.

By Marriott's method, samples of alveolar air were obtained by rebreathing into a rubber bag. The CO_2 content of this sample, presumably equal to that of the alveolar air, is also proportional to the carbonic acid content of the plasma, since the carbonic acid and the bicarbonate always vary in a parallel manner. In compensated acidosis the alveolar (rubber bag) CO_2 would also parallel the plasma bicarbonate and would serve as a measure of the bicarbonate concentration.[61] Van Slyke,[62] however, devised a method by which the bicarbonate of the plasma was measured directly. If acid is added to a solution of sodium bicarbonate, a certain amount of CO_2 is liberated. The amount of liberated CO_2, which can be measured, depends on the amount of bicarbonate present. Hastings later elaborated a method of testing the pH of the blood directly.[63] Van Slyke was able to postulate at least 9 different types of acid or alkaline states from the theoretically possible relationships of H_2CO_3-$BHCO_3$; in many instances actual clinical entities were found which fitted each of the theoretically possible types.

Schmidt in 1885 had been the first to find evidence of an acidosis in diarrhea.[47] His methods for the determination of blood calcium, magnesium, sodium, chloride, and oxy-

hemoglobin were crude and necessitated large amounts of blood. When Holt, Courtney, and Fales[64] investigated the same subject, they did balance experiments instead, since they were dealing with children from whom only small amounts of blood were available. Finding a greater loss of base than of acid in both urine and stool, they too, came to the conclusion that diarrhea, this time in infants, was often associated with acidosis. Czerny,[65] the clinician, was the first to appreciate fully the similarity between diarrheal acidosis, diabetic acidosis, and the acidosis in Walter's dogs. It was Czerny's recognition of this similarity which stimulated Howland and Marriott to proceed further along these lines.

Howland and Marriott studied a group of infants with severe diarrhea and proved the presence of acidosis by all the methods then at hand: (1) a lowering of the CO_2 tension of the alveolar air, (2) an increase in the hydrogen-ion concentration of the blood serum, (3) Sellards' test for the reaction of blood serum, (4) measurement of the amount of alkali required to alter the reaction of the urine, and (5) measurement of the diminution of the combining power of the hemoglobin with oxygen.[61]

That the human body was no mere test tube was quite obvious from the beginning, and investigators very early began to study physiologic phenomena associated with the chemical changes. Toxicity and shock as the physiologic result of diarrhea were first mentioned in 1876 in an article by Edward Waldo Emerson.[66] A quotation from the original article will best serve our purpose: "The collective symptoms of paleness, coldness, cyanosis of all the surfaces, and probably too of the lungs, together with the internal objective and subjective heat and the immense activity of movement and transudation in the bowel, the suddeness of the collapse and the apparent emaciation, and the equal suddenness of the recovery and reappearance of heat and *turgor vitalis* would alone demonstrate . . . that the main pathologic condition was an entire change of circulation, namely, engorgement of the abdominal at the expense of the peripheral and respiratory organs. In fact, it is a condition in many respects analogous to two other circulatory disturbances, syncope and shock, the pathology of which states are set forth at length in an interesting article in the *Practitioner* for October, 1873, by T. Lander Brunton."

Although Blackfan was the first to demonstrate the importance of restoring the body fluids and electrolytes with intraperitoneal infusion, it was Schloss[67] in 1918 who performed the studies which form the basis for our modern concept of the physiology of acidosis and intestinal intoxication. His report was based on a study of 46 infants with intestinal intoxication, together with 30 normal infants used as controls. In the sick infants, he uniformly found a marked increase in the nonprotein nitrogen and urea of the blood, together with other signs of renal insufficiency. However, since histologic examination of the kidneys showed no organic basis for defective action, he postulated that the impairment of kidney function was due to the absence of enough water to form urine. The lack of water was due to its great loss in the stools, the distaste of the patients for water, and to the tendency of the patient to vomit what he drank. There is consequent hemoconcentration which together with a diminished blood volume, also proved by Marriott, halted normal function in the kidney. We know from the work of Starling[68] that with a colloidal osmotic pressure of the blood greater than the arterial pressure in the renal glomeruli, secretion of urine by the kidney ceases. The combination of impaired excretion, dehydration, and losses through the intestinal secretions resulted in a general disturbance of ionic balance. As pointed out by Powers,[69] it is the common presence of hemoconcentration which causes a similar clinical picture in diseases with such diverse causation as fever of the newborn, Asiatic cholera, severe burns, high intestinal obstruction, traumatic and histamine shock, lethal war-gas poisoning, certain cases of influenza, and induced dehydration in animals.

As a result of this work a working explanation of the cause of acidosis in acute diarrhea could now be elaborated. Czerny had originally suggested that it might be due to the entry of organic acids into the blood, but Howland and Marriott had not found enough of an increase to make this explanation plausible. Steinitz[70] suggested that the cause might be a loss of alkalies in the stool. Although the experiments of Holt, Courtney, and Fales did show a predominance of alkalies in the stool, there was also an increase in chlorides. Howland and Marriott[61] hypothecated that the acidosis was due to a renal retention of acid sodium phosphate and actually demonstrated an increase in the phosphate content of the serum in a few cases. The work of Schloss[67] substantiated this hypothesis. In the same article Schloss applied the term *intestinal intoxication* to the entire syndrome of toxic symptoms which followed some, and caused the rest, of the chemical disturbances and renal failure resulting from diarrhea. The role of the kidneys in the regulation of body neutrality has been further analyzed. The kidneys serve by stabilizing the plasma concentration of bicarbonate-bound base at a level of 25 to 27 mEq. per liter. This is accomplished by two different processes. The first is by salvage of the bicarbonate which filters through the glomeruli. The efficiency of this mechanism is such that, although large quantities of bicarbonate are excreted in the urine following its ingestion, only 0.1 per cent of that filtered through normally appears in the urine. The second mechanism is the substitution of hydrogen or ammonium ions for sodium ions in the tubular urine. By this process large amounts of metabolic acids can be excreted without sacrificing body sodium.[71] The remarkable ability of the kidneys to conserve essential fixed base was demonstrated quantitatively by Gamble in 1947.[72, 96]

These outstanding accomplishments in so short a period depended largely on the elaboration of chemical methods. In no other field is the relationship more clearly indicated between "pure" science and its implementation. Few partnerships have been more significant than that between the chemist interested in medicine and the internist interested in chemistry. Back in 1850, Schmidt[47] had carried out elaborate studies of the composition of human blood. Indeed, he was the first to point out the presence of a preponderance of potassium in the red blood cells and of calcium in the serum. The chemical methods employed, however, were such that large amounts of blood were required, amounts which made it impractical to study closely the changes resulting from human disease. Such studies awaited the elaboration of accurate techniques requiring only small amounts of blood. There was needed a science of microchemistry.

To fill this need, such men as Bang,[73] Folin-Wu, and Van Slyke elaborated micromethods for determining the nitrogen-containing elements in the blood. To fill this same need, and also the requirements for balance studies, there soon followed elaboration of micromethods for determination of the inorganic constituents of the blood.

Sodium, the chief basic constituent of the blood plasma, had in the past been determined by the isolation of sodium and potassium as chlorides, the direct determination of potassium as the chloroplatinate, and then by assuming the difference to be sodium. Methods, however, were soon elaborated for the direct determination of sodium by the formation of insoluble, measurable compounds: dihydroxytartaric acid by Fenton[74] in 1898, sodium cesium bismuth nitrite by Doisy and Ball[75] in 1910, uranyl magnesium sodium acetate by Streng,[76] sodium uranyl zinc acetate by Barber and Kolthoff.[77] Potassium pyroantimonate had been used for a long time to detect sodium, and Kramer and Tisdall[78] first used this reaction for the determination of small amounts of sodium in unashed serum. For the determination of potassium in the serum Kramer and Tisdall used the established method of precipitating potassium sodium cobaltinitrite, but they determined small amounts accurately by using permanganate to determine the amount of nitrite.[79] Methods for determining total base were elab-

orated by Stadie and Ross[80] and by Van Slyke, Hiller, and Berthelsen.[81] The method of chloride evaluation, rendered difficult by the need to remove the protein, was modified by Kramer to require only 0.2 c.c. for its determination.[82]

Armed with methods necessitating only minute amounts of blood, the entire dynamic chemical picture during and after diarrhea could be visualized. The whole complex relationship of anion-cation balance and the constituents of the total fixed base could be studied minutely. The final culmination of this progress in methodology came with the perfection of the flame photometer. With this instrument, determination of potassium and sodium can be made almost instantaneously, so that the actual momentary changes in disease can be followed.

The elaboration of the chemical picture in diarrhea made it possible at least to attempt a logical approach to treatment. Such an approach was outlined by Powers[69] and consisted of four points: administration of fluids, transfusion of blood, the withholding of food for a period, and the subsequent addition of food in small and slowly increasing quantities.

This perfection in methods has shed light on some disease entities not directly related to diarrhea. Darrow[83] was able to prove that the cell membrane was not entirely impervious to the passage of potassium ions as had always seemed to be the case. He demonstrated passage of potassium ions into the extracellular fluid, as sodium ions from that matrix found their way into the cell. When the body fluids are restored as the patient improves, there results a relative decrease in cell potassium. He also speculated on the possible effects of a low potassium content of the blood on familial periodic paralysis and on myocardial damage. In 1924 Wilkins and Kramer[84] had demonstrated electrocardiographic changes resulting from hypokalemia. Experimentally, Follis[85] was able to produce cardiac and renal lesions following prolonged feeding of a diet deficient in potassium. Gamble[86] in 1948 reported a case of an infant suffering from diarrhea resulting in a low serum potassium, and demonstrated electrocardiographic changes which disappeared as a normal serum potassium was achieved. Gavan[87] was able to report a similar case. The methods by which a hypokalemia could be prevented and a more rapid restoration of cellular composition be achieved, were summarized by Gavan and Darrow[88] and again by Darrow.[89] The significance of a normal potassium level, and also the importance of loss of phosphorus and other electrolytes were also stressed by Rapaport.[90]

Although the efforts of the Flexner group and those who applied their findings brought about a tremendous drop in infant mortality from diarrhea, there still remained a hard core of infant deaths due to this illness. The vital statistics of New York City show that, while in the 25 years, 1923-1947, the death rate from diarrhea in infants 1 month to 1 year of age dropped from 8.7 per hundred thousand to 0.9, the corresponding figures for babies under one month of age were 1.1 and 0.5. The death rate from diarrhea has not decreased in babies during the newborn period to the extent that it has in older infants.

In New York City in the years 1934-1938, there were 924 deaths from a type of diarrheal disease which was either new or had not been previously distinguished. It was first described by Rice, Best, Frant, and Abramson[91, 92] who called it epidemic diarrhea of the newborn, and who carefully excluded from this group those cases of diarrhea caused by known pathogenic organisms. The disease occurred only in the first 4 weeks of life, appeared exclusively in hospital nurseries, among both ward and private patients, and among the breast-fed babies as well as those bottle-fed.

From the amount of interest aroused by this report, the disease has been and continues to be rampant in many hospitals throughout the country. The etiology has never been firmly established. In 1937, at the presentation of the paper by Rice, Dr. Joseph Golomb suggested during the discussion that the etiology might be a filterable

virus. In 1941, Lyon and Folsom[93] made the same suggestion on the basis of the occurrence of an epidemic while influenza was spreading through the hospital population. In 1943, Light and Hodes[94] were able to transmit the disease to calves by using a filtered suspension of stools from infants suffering with the disease. This they could do during four different epidemics, and they could furthermore carry the infection through a series of calves. They could not find the virus in the stools of normal infants or calves. The possibility of a virus etiology for this disease has been further strengthened by the work of Buddingh and Dodd[95] who demonstrated the development of immunity in convalescent infants by showing protective antibodies in their serum against keratitis in rabbits which developed by scarification with filtered material isolated from diarrheal stools.

It is now generally recognized that diarrhea may be caused by specific types of *Escherichia coli*.[97] The first attempts to identify these strains were in 1912 by differential sugar fermentation,[98-100] and soon after a serologic type was isolated,[101] albeit not clearly. In 1951, a clearer antigenic analysis was completed[102] and the *E. coli* were classified according to O, K, and H antigens.[103] By this antigenic analysis several strains have been quite definitely identified as the causative agent of infantile diarrhea.

The history of diarrhea as we have outlined it here reflects the general history of the development of modern medical knowledge. First, there was the accumulation of clinical observations by numerous observers over thousands of years. Then came increasingly skillful postmortem examinations, with gradual accumulation of correlations between symptoms and organic changes in the involved organs. Later, development of the sciences of bacteriology and immunology made possible finer and less obvious differentiation among the various disease entities. Increasing knowledge of chemistry made such differentiation even more specific, while the development of microchemical methods made possible accurate and rapid determinations, even when minute amounts of blood were available so that chemical and physiologic correlations could be followed during the actual disease process.

Finally, with the development of further knowledge of virus infection, there are indications that this process will extend even further our basic knowledge of this disease, particularly during the newborn period.

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CLINICAL PATHOLOGICAL CONFERENCE

THE CHILDREN'S HOSPITAL MEDICAL CENTER, BOSTON, MASS.

Sidney Farber, M.D., Editor
Gordon F. Vawter, M.D., Assistant Editor

THIS 7-year, 2-month-old Negro boy was admitted initially with complaints of easy fatigability and anorexia of 3 months' duration, a slightly erythematous scaly and pruritic rash over the face, elbows, and knees for 2 months, and weakness on walking of several weeks' duration. He required assistance in climbing stairs, walked on tiptoe, and complained of transient nonradiating left thoracic pain, unrelated to exercise or respiration. There had been no apparent antecedent illness and no known fever.

The maternal grandfather had diabetes and the mother had glycosuria with each pregnancy. There were 4 siblings, 12 to 3 years of age, who were well except that the oldest was "allergic to many things."

Examination revealed temperature 99° F. (rectal), pulse 100 per minute, and respirations 20 per minute. He was a thin boy with scaly skin over the extensor surfaces of the joints, especially the elbows, knuckles, and knees (Fig. 1). In addition, there were periorbital and perioral puffiness and white patches on the oral mucosa. Ears, nose, throat, heart, lungs, and abdomen were normal. There was some swelling about the knees, but no heat or tenderness. There was striking generalized weakness and the muscles were firm and somewhat tender. Fifteen to 30 degree limitation of flexion was noted at the elbows and knees.

Laboratory data were as follows: hemoglobin 11.7 Gm. per cent; white blood count 5,600 per cubic millimeter, with 56 per cent polymorphonuclear leukocytes, 35 per cent lymphocytes, and 7 per cent monocytes. Two absolute eosinophil counts were 193 and 220 per cubic millimeter. The corrected sedimentation rate was 9 mm. per hour on 2 occasions. The urine showed pH 6.0; specific gravity 1.025; albumin, trace; acetone, 3 plus on admission; 0 thereafter. Serum contained calcium, 10.8 mg. per cent. The bone age was 6 years and there was slight demineralization. A chest x-ray showed right nonspecific prominence of the bronchovascular markings, indistinct soft tissue planes, and normal joints and spine. Hemolytic *Staphylococcus aureus,* phage type 29, was cultured from a fluctuant area which developed over the occiput during the initial hospitalization. A lupus erythematosus cell preparation was negative.

After a skin and muscle biopsy the boy was provided with casts for the extremities and given physiotherapy during and after his 4 weeks' hospitalization. Two and a half

months after discharge he was readmitted with increasing severity of the entire disease process. His weakness had progressed and for 10 days he had had difficulty in eating and swallowing. He drooled occasionally, although choking and aspiration were denied. He had fever up to 104° F. (oral).

He was a thin boy (45 pounds, fifteenth percentile) with the scaly rash previously described, and he was in no distress. There was a medial scleral hemorrhage on the left, and periorbital edema. The heart extended to the midclavicular line with a diffuse apical impulse and a blowing grade II apical systolic murmur. The temperature was 100° F. (rectal), pulse 108 per minute, respirations 42 per minute, and blood pressure 120/90 mm. Hg. There was tenderness over the left upper arm. Some râles were heard posteriorly at the pulmonary bases. There was a small amount of fluid demonstrable in the right knee, and thickening of the tissues around this joint. Weakness and limitation of motion had progressed.

Laboratory data showed: hemoglobin varying from 10.3 Gm. per cent initially, to 7.7 Gm. per cent terminally; white blood count 7,600 to 26,050; polymorphonuclear leukocytes 51 to 65 per cent; band forms 0 to 28 per cent; lymphocytes, 32 to 4 per cent; monocytes 12 to 1 per cent; eosinophils 1 to 0 per cent. Platelets were adequate by smear. Urinalyses were within normal limits 4 times. The nonprotein nitrogen of blood was 16 to 41 mg. per cent. Albumin/globulin ratio was 4.4/2.5 Gm. per cent. The serum electrolytes were normal except that chloride fell to 89 mEq. per liter, terminally. Studies of hepatic function one week after admission showed prothrombin 79 per cent of normal; cholinesterase 49 mμ per cent (normal 30 to 60 mμ per cent); thymol turbidity, thymol flocculation, and cephalin-cholesterol flocculation, negative. On the chest x-ray there was marked enlargement of a globular heart, slight pulmonary congestion, increased density in the right upper lobe, considerable osteoporosis, and marked soft tissue swelling of the elbow. With barium swallow, the aryepiglottic recesses retained the contrast material; the esophagus appeared atonic; the stomach and small intestines were nor-

Fig. 1. Characteristic hyperkeratotic scaly dermatitis, here involving knees.

mal. Later x-rays showed a decrease in heart size. A lupus erythematosus cell preparation was again negative. Two electrocardiograms were normal.

Treatment with penicillin and cortisone was begun (cortisone 100 mg. 3 times per day for 3 days, and 50 mg. 3 times per day, thereafter). He continued febrile. Vital capacity fell to 300 ml. (normal, 1,500 ml.), and tidal volume was 50 to 75 ml. Edema of the legs developed. Aluminum hydroxide gel was begun when the stools became guaiac-positive. Tube feedings were required after one month in the hospital. Three days later he was in extremis, vomiting, with distended and tympanitic abdomen, and with free air under the diaphragm radiologically. He died 2 days later.

DR. CHARLES D. COOK.* In the initial phase of this boy's illness, with only the nonspecific symptoms of fatigue and anorexia, it would be necessary to consider such general groups of diagnoses as collagen diseases, malignant diseases, or chronic low-grade infections. However, this child soon developed muscle weakness and skin lesions over the extensor surfaces of the joints. The weakness alone might have suggested neurological disease, such as polyneuritis or even poliomyelitis, or might have pointed toward a variety of muscular disorders, including progressive muscular dystrophy or myasthenia gravis. The muscle tenderness and induration described indicated that an inflammatory process, some sort of myositis, was probably the underlying lesion. If the process had been more acute, if the child had had more fever and an eosinophilia, one might have been briefly tempted by the diagnosis of trichinosis. In view of the entirely diagnostic skin lesions described, and the muscle weakness, however, there can be only one diagnosis: dermatomyositis or myositis universalis acuta infectiosa, as it was once called.

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Some of these children present with only periorbital edema, with or without a violaceous discoloration of this region. Frequently an ophthalmologist or allergist sees the child before the onset of obvious myositis. The facial rash, with its butterfly distribution, may be confused with that seen in disseminated lupus erythematosus but this latter condition rarely has specific muscle weakness, and usually has evidence of nephropathy, as well as a positive lupus erythematosus cell preparation. In addition, the dermatitis of the extensor surfaces of the joints, when present, is diagnostic and more specific, probably, of dermatomyositis, than the histopathology.

In the atypical case, a number of differential diagnoses would have to be considered. Walton and Adams[1] have recently described and discussed in detail polymyositis and included dermatomyositis in this general group. Their list of differential diagnoses includes myoglobinemia, Werner's syndrome, sarcoidosis, primary generalized myositis fibrosa, progressive myositis ossificans, progressive diffuse sclerosis, and relapsing myositis. Whether or not polymyositis is really related to dermatomyositis remains to be decided when more is known about the pathogenesis of the disease process(es). However, certain (perhaps entirely arbitrary) differences exist. For example, in polymyositis there are no skin lesions, there is good prognosis compared to 50 per cent mortality for dermatomyositis and there is a frequent apparent association with streptococcal infections not found with dermatomyositis. Contractures are a frequent complication of the muscle involvement in dermatomyositis and are rare in polymyositis.

There are several other interesting features about this boy's primary illness which we should consider—for example, the finding of joint effusion. Except for this child, I know of no other in our series with objective findings of primary joint involvement. However, Pearson[2] reported 6 of 17 patients with dermatomyositis, all adults, who had arthritic effusions; the arthritis, which was

never severe, involved primarily the small joints. In 5 of the 6 cases with joint involvement, the latex fixation test was positive, while in only 1 of 5 cases without joint involvement was it positive.

Stertz, in 1916, first noted the relation between dermatomyositis-like lesions and malignant disease. We have seen at least 1 case of leukemia associated with lesions which simulated dermatomyositis, and at least 51 cases of malignancy coexisting with dermatomyositis had been reported in the literature by 1955. For instance, 3 cases are reported by Sheard.[3] We have also had 2 cases of agammaglobulinemia with similar dermatomyositis-like findings. The term "dermatomyositis-like" should be stressed because, while there are certain clinical and histologic similarities between true dermatomyositis and these combined syndromes, there are important differences; thus, there is little or no muscle weakness and the course of the dermatomyositis-like condition tends to be benign in the latter conditions. The etiological relation between the skin and muscle abnormalities and those other conditions might well provide us with knowledge concerning the pathogenesis of the disease, but, thus far, has only added to the mystery.

Dermatomyositis is often considered one of the "collagen diseases" and hence is thrown into a group with rheumatic fever, rheumatoid arthritis, disseminated lupus erythematosus, scleroderma, and possibly also anaphylactoid purpura and others. Some of these, particularly disseminated lupus erythematosus and rheumatic fever, are called hypersensitivity diseases but there is, at the moment, no evidence which really substantiates, except by vague analogy, this concept for dermatomyositis. Several years ago Bardawil and co-workers[4] reported finding in disseminated lupus erythematosus, scleroderma and dermatomyositis, an abnormal gamma globulin which combined with intranuclear material. This finding has been substantiated for disseminated lupus erythematosus, but he has not been able to demonstrate this in any of our patients with dermatomyositis.

Fig. 2. X-ray of elbow. There is loss of normal tissue planes with atrophy of fat, and probable periarticular involvement.

Also of interest is the recent work on serotonin in rheumatoid arthritis and disseminated lupus erythematosus. It has been found by Scherbel and Harrison[5] that there is apparently a definitely abnormal sensitivity to serotonin in those conditions. Furthermore, it has been demonstrated that repeated injections of serotonin in rats produces scleroderma-like proliferation of collagen tissues. Since serotonin affects blood vessels and since blood vessels are frequently the first tissues involved in collagen diseases, these leads need further exploration; certainly, studies of serotonin sensitivity should be carried out in dermatomyositis. At the same time, mast cells[6] which apparently produce serotonin and are present in connective tissue should be studied.

With that information about this disease, dermatomyositis, in general, what about the complications which this boy had which led to his death? The child had a subcutaneous abscess; the skin in this condition tends to be edematous and in many areas avascular, and pressure sores and ulcers and secondary infection occur. He did, as do many of these children, develop a mild to moderate cardiac murmur. There is usually relatively little involvement of the myocardium although in this case, with cardiac enlargement, there may be more than usual.

Fig. 3. There is evidence of cardiac enlargement in the chest x-ray 1½ months before death.

As he went into progressive respiratory failure he evidently developed bronchopneumonia. At the same time the striated muscle of the upper esophagus was involved in the process and led to difficulties with deglutition. In addition, he presumably developed an area, or areas, of erosion of the mucosa of the gastrointestinal tract, and began to bleed. One of these lesions finally perforated and led to peritonitis and his final death. Although some of the children with dermatomyositis have had perforations of the esophagus, in this case the perforation was apparently lower, probably in the small intestine. Many of these children, if they survive long enough (usually several years) will develop deposits of calcification in the region of the necrotic muscle[7]; I see no evidence that this child did. Perhaps Dr. Neuhauser can help us at this point.

Dr. E. B. D. Neuhauser. On his first admission, the heart and great vessels, the pulmonary fields, and the hepatic and splenic shadows were normal. I believe that the bones were slightly osteoporotic and that soft tissue changes were evident even then, but they are much more clearly shown at the second admission. The bones appear "washed out" from osteoporosis. Clarity of the outlines of the soft tissue planes is completely lost; the fat pads have disappeared with homogeneous density through all the subcutaneous tissue. In a film of the elbow there is thickening of the periarticular soft tissue (synovia), and possibly some increase in fluid (Fig. 2).

We have no films of a fluoroscopic study of the swallowing function described by Dr. Wittenborg. The barium remained too long in the pyriform sinuses. The esophagus itself appeared deficient in peristaltic activity, and barium passed through slowly. There was always quite free reflux of the barium back from the stomach into the lower esophagus.

In a film of the chest made one and a half months before death (Fig. 3), there is, compared with the original films, striking increase in the size of the cardiac silhouette, with nonspecific globular contour which we associate with cardiac dilatation and myocardial weakness. In the pulmonary field there is a very definite but not marked evidence of congestion, especially in the basal and medial thirds.

One cannot see any definite sign of diaphragmatic weakness. About 4 weeks before death there was some evidence of clearing of the lung fields, except for a mottled den-

Fig. 4. Four days before death pulmonary infiltration, probable mediastinitis, and air under the diaphragm are additional features.

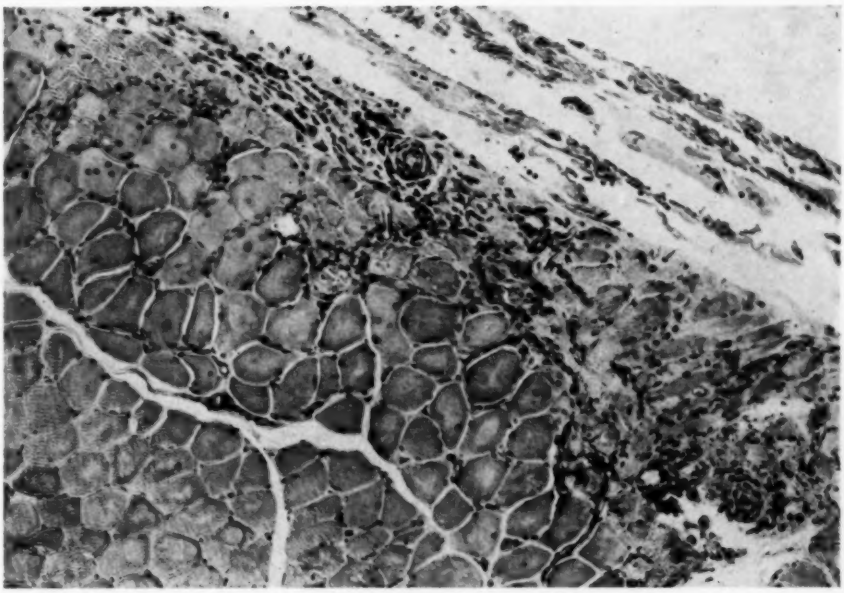

Fig. 5. Muscle biopsy shows characteristic lesion at junction of muscle and perimysium. (Hematoxylin and eosin. Original magnification ×250.)

sity in the right upper lobe, which may represent aspirational pneumonia. In a film 4 days before death (Fig. 4) the mottled densities now involve the entire right lung and, to a lesser degree, the left lung, where there is also a small amount of fluid. Difficult to see is a great mottled density behind the heart, which could well represent a basilar pneumonia or a low mediastinitis associated with esophagitis. In addition, there is a very extensive collection of free air beneath the diaphragm.

DR. COOK. Perhaps then, as Dr. Neuhauser has suggested, a certain amount of pulmonary congestion is present, together with some type of cardiac involvement. Although cardiac involvement was recognized in dermatomyositis as early as 1903 by Oppenheimer,[8] the process is usually mild from a clinical point of view and I, personally, know of no case in which death has appeared to be primarily cardiac in origin.

As to therapy, I know of nothing which could have prevented this child's downward course. Those dealing with adults with this disease are enthusiastic about the use of adrenocorticotropic hormone, cortical steroids, and/or testosterone. Our experience in 25 patients (we have seen about 25 or 30 patients with this disease since 1950) suggests that steroid therapy provides symptomatic relief from pain and fever and toxicity but rarely, if ever, significantly alters the course of the disease—except in the situation where such treatment produces serious or fatal reactions in itself. A recent paper[9] proposes the use of EDTA for the treatment of the calcinosis which develops in these patients. We have had no experience to allow us to evaluate such a suggestion.

DR. CHARLES A. JANEWAY. The first patient I was shown, on a recent trip to India, was one with dermatomyositis. The disease is seen all over the world and is particularly common among children.

We give large doses of steroids to patients

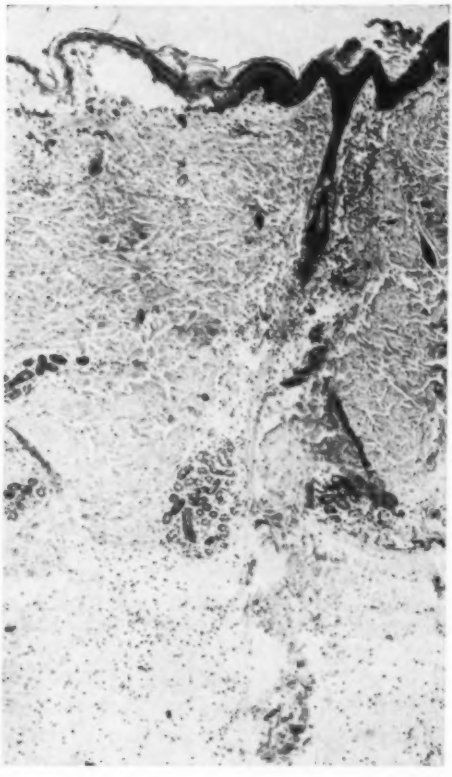

Fig. 6. Vesiculation, hyperkeratosis, mild chronic dermatitis, and dermal edema involve skin at time of death. (Hematoxylin and eosin. Original magnification ×85.)

suffering from a number of different diseases, but I do not recall that perforation of the alimentary tract has occurred in them, certainly not with the frequency seen in dermatomyositis.

DR. COOK. Perforation of abdominal viscera occurred in these patients occasionally, even before the days of treatment with adrenal corticoids.

DR. JONATHAN COHEN. I would agree that polymyositis and dermatomyositis are difficult to distinguish, especially when the skin lesions are very mild or grossly unrecognized, but one should emphasize that either of these conditions may present a wide spectrum of severity, from the mildest to the most devastating disease. On the other hand, occasional patients presenting with severe disease may go into remission or recover.

DR. JANEWAY. A few weeks ago I saw a child with dermatomyositis whose sibling had diabetes. His doctors were considering withholding steroids from the patient, for fear of lighting up a latent process. I notice, too, that our patient's mother is diabetic.

DR. COOK. This association is very intriguing, but we have not recognized it in any of our other patients with dermatomyositis.

DR. VAWTER. One reads that patients with dermatomyositis who have eosinophilia have a better prognosis than those who do not.

DR. COOK. About one-third of the patients do have eosinophilia, but I am not sure of a close correlation with prognosis.

DR. SIDNEY FARBER. In connection with Dr. Cook's comments upon leukemia and dermatomyositis, I would like to remind you of a child with both diseases who, shortly after ACTH first became available, was given the medication to treat the dermatomyositis. He had an extraordinary improvement of both his diseases, with remission established in the leukemia within 18 days of the beginning of treatment.

Dr. Vawter, would you present the findings?

DR. VAWTER. There is a plethora of lesions in this case which comprise a classic picture of *dermatomyositis.*

Biopsies of skin and muscle obtained on first admission show minimal and histologically nondiagnostic changes in skin consisting of mild hyperkeratosis, minimal dermal edema, and minimal round cell infiltrates perivascularly in the dermis. The lesion involving muscle (Fig. 5) is, however, quite characteristic and probably diagnostic. At the interface between perimysium and the outer portion of the muscle fasciculus lies the battleground, composed of round cells, macrophage elements, and occasional cells of plasma cell type. Mast cells were not found, although special preparations (not done in this case) are sometimes required to demonstrate them. In the zone of infiltra-

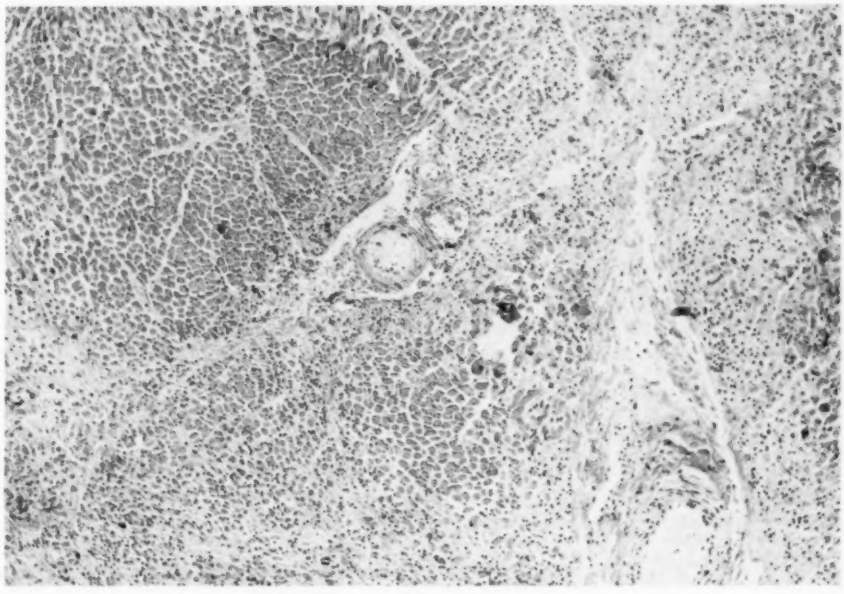

Fig. 7. Terminally, vascular occlusions and infarctlike necroses are added lesions in muscle. (Hematoxylin and eosin. Original magnification ×80.)

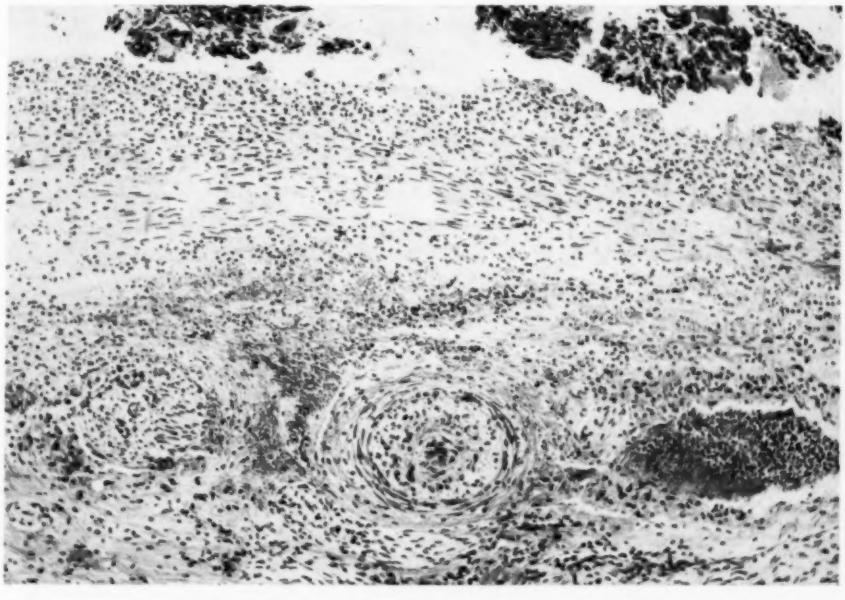

Fig. 8. In esophageal wall, near site of perforation, there are active perivascular necroses and ancient recanalized arterial occlusions associated with overlying ulceration. (Hematoxylin and eosin. Original magnification ×160.)

tion, the muscle fibers are disintegrating, whereas those in the center of the fascicle are spared, possibly because vasculitis is not yet prominent at this time and in this place. However, the general impression is one of degeneration, in view of the rather indolent appearance of the inflammatory cells mobilized here.

At the time of autopsy there was a great deal of activity in the skin, with edema and hyperkeratosis, in epidermis (Fig. 6) where some of the lesions showed suprabasal vesiculation, and in the muscle (Fig. 7) where vasculitis, vascular sclerosis, and vascular thrombosis were prominent and associated with actual infarction of large areas of muscle. There was associated loss of fat and fibrosis. The latter process produced a striking change, so that tissues not specifically muscular, such as perirenal areas, present a fibrosis ending in a state where the child and some of the viscera were almost literally encased in scar. There was not much evidence, then, that treatment ameliorated the disease.

As is so characteristic in these patients, vasculitis was also prominent along the alimentary tract (Fig. 8), in esophagus and cecum, and in small bowel. In the former sites (esophagus and cecum the consequent ischemic necrosis led to perforation, with development of generalized purulent peritonitis and mediastinitis, which ruptured into the left pleural space, producing a pyopneumothorax. These lesions, in the presence of some aspiration pneumonia, provide obvious causes of death and thrust a mild healed epicarditis and mild interstitial myocarditis of nonspecific character far into the background.

The esophagus and small bowel, especially duodenum, have been common sites of perforation in these patients. The presence of vasculitis and ischemic necrosis in and around these lesions indicates that this is one primary pathogenetic mechanism for perforation, although one cannot completely exclude a role of steroid therapy in suppression of normal inflammatory response to the initial injury.

Unlike many cases of dermatomyositis, the spleen in this instance was small, the white pulp somewhat depleted, but plasma cell infiltrations were apparent.

There were lesions in nerve roots and spinal cord, associated with vascular sclerosis, and probably anemic atrophy of neural tissue. One wonders if this relates to his complaint of pain in the back.

DR. SIDNEY FARBER. Dr. Banker, would you comment?

DR. BETTY Q. BANKER. First, I should like to stress one point. I think that the dermatomyositis of children, with its vasculitis and its perimysial reaction, is quite unlike the dermatomyositis of adults, where one often gets the impression of necrosis of single muscle fibers causing a secondary inflammatory

Fig. 9. At junction of esophagus and stomach there is a large discoid ulcer with ragged base which has perforated, with mediastinitis and pleurisy.

response, and where vasculitis is often not prominent. Indeed, this childhood dermatomyositis, for me, constitutes a unique disease of muscle unlike any counterpart yet known in animals, and unlike the polymyositis of infants, children, or adults where, again, the type of lesion appears to be a degeneration of single muscle fibers, almost as in a muscular dystrophy, and displays marked variation in size of muscle fibers with all fasciculi of any given muscle diseased.

This case might also be called a neuromyositis in view of the vascular involvement of nervous tissue, centrally. These neural lesions probably contribute their part to the muscular disease in this patient with interference in normal regeneration in the injured muscle.

DR. SIDNEY FARBER. What is your concept of the disease, Dr. Banker?

DR. BANKER. I do not think we will be very near to knowing until we can reproduce a similar disease at will. My concept is that of a diffuse vascular disease with selective organ or tissue involvement. We will have to work hard to discover whether hypersensitivity plays a role or not.

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COMMENTS ON CURRENT LITERATURE

Ophthalmic complications in favism

THE mechanism by which hemolysis of red cells occurs in favism and in some hemolytic anemias that appear to be dependent upon extrinsic factors is not completely understood as yet. Under certain circumstances clinical hemolysis seems to result from exposure to toxic substances in those individuals who have a marked erythrocyte deficiency in glucose-6-phosphate dehydrogenase and an unstable erythrocyte metabolism.[1, 2, 3] There is evidence that in favism and certain drug-induced hemolytic anemias the mechanism of red cell damage may be analogous.

Favism in its more severe form is characterized by hemolytic anemia, oliguria with hemoglobinuria, and jaundice. Symptoms develop in susceptible individuals who come into contact with the broad bean, *Vicia fava,* either by inhaling the pollen of the flowering plant or by eating the ripened bean. This broad bean, also known as the fava bean, the horse bean, etc., is a common food in some parts of the world, notably Southern Europe. Its cultivation in the United States has been increasing in recent years. The seasonal occurrence of favism is coincident with the flowering of the plant in spring or early summer, and with the use of the beans as food at the time of harvest. In some instances the dried bean also has been used as a winter food. However, when dried the bean loses much of its capacity to evoke reaction in the human subject. Cases of severe asthma and hay fever have been observed in some farm workers or in others exposed to the pollen.

Whatever the route of exposure, by pollen inhalation or by the ingestion of raw or cooked beans, the clinical manifestations vary widely in severity. In milder cases especially in adults, the condition may be abortive, with headache, nausea, pallor, and transient pain in the extremities, or merely headache and slight fever, with malaise for a period of a few hours, in which case the clinical condition is suggestive of migraine. Varying degrees of severity have been observed in children[4]: a mild form which consists of moderate anemia, icterus, and slight hemoglobinuria; a grave form with weakness, prostration, marked pallor, moderate icterus, scant and bloody urine, diarrhea, and vomiting; and a fulminating form seen largely in very young children with intense anemia, hemoglobinuria, and shock. In this severe form petechiae and ecchymoses may be present. Special forms which have been described include cases with icterus as the only evidence of erythrocyte damage, and an urticarial form accompanied by intense itching. Rare instances of blindness as a manifestation have been reported.

In this connection recent case reports from Greece are of special interest. These reports from the Pediatric Clinic of the University of Athens are by Choremis, Joannides and Kyriakides[5] and concern severe ophthalmic complications in favism.

Favism is relatively common in Greece; every spring season a number of children are admitted to this clinic suffering from variable degrees of hemolytic anemia and other manifestations of favism. In the present report 2 patients are described who developed serious ophthalmic complications with blindness.

The first of these patients was a 3-year-old boy who developed malaise, vomiting, oliguria and hemoglobinuria, and jaundice 24 hours following the ingestion of broad beans. On admission to the hospital a few hours later, the child was in coma, not responding to light, and deeply jaundiced. The temperature on admission was 39.6° C., respirations 60 per minute, pulse 180 per minute, and blood pressure 75/45 mm. Hg. The lower limbs were spastic; bilateral extensor plantar reflex was elicited with ease. Both liver and spleen were palpable 3 cm. below the costochondral margin. For about 12 hours the child's urine had been scanty and dark red; a specimen obtained on admission contained large amounts of hemoglobin. Treatment consisted in blood transfusion and parenteral fluids; in the ensuing 24 hours after admission the patient received a total of 1,000 ml. of whole blood, plus 500 ml. of equal proportions of saline and glucose, 5 per cent. Prednisone, 5 mg., and aspirin were administered initially, and the child received in addition 200,000 units of penicillin every 6 hours. There was no known sensitivity to penicillin or other antibiotics. Laboratory studies at this time revealed the following: red cell count, 2,300,000 per cubic millimeter; hemoglobin 6 Gm. per cent; bilirubin, 5.8 mg. per cent (indirect 2 mg. per cent); and blood urea, 66 mg. per cent. For the 3 days following the patient was under close observation and supportive care, with whole blood transfusions as necessary. Diuresis gradually became normal, and the urine cleared completely within 4 days. However, the child was still comatose, and an electroencephalogram at this time showed irregular slow waves in all leads. On the fifth hospital day widespread ecchymoses appeared on the buttocks and legs, and the child vomited "coffee-ground" material. His general condition appeared to be deteriorating rapidly. Laboratory findings at this time included: hemoglobin 5.35 per cent, white blood cells 26,000 per cubic millimeter; platelets 26,000 per cubic millimeter; bleeding time, 8 minutes, and clotting time within normal range. During the next few days, however, the patient came very slowly out of coma; the hemoglobin rose to 8 Gm. per cent and the platelets to 60,000 per cubic millimeter. New ecchymoses did not appear and the child's general condition improved considerably; however, he was completely blind. In less than 3 weeks following the original episode the child appeared normal except for the ophthalmic condition.

Periodic ophthalmologic examinations were possible from the third hospital day. On this day the pupils were mydriatic and did not respond to light; the vitreous body was clear. On funduscopic examination the discs were prominent with blurred margins and distended and tortuous veins. Widespread retinal and preretinal hemorrhages were apparent mainly in the posterior pole. One week later the pupils were still mydriatic, and did not respond to light. The fundi could not be visualized because of infiltration of the hyaloid with blood. The patient was completely blind. Examination performed 3 weeks after admission to the hospital revealed no significant change, although the child could now distinguish light from darkness. One month following admission the fundi were still not visible, although there had been some clearing of the vitreous body. Ophthalmologic examinations performed periodically throughout the hospital stay of nearly 4 months revealed that organization of the hemorrhages had occurred, with only minimal clearing of the vitreous body.

The second case was that of a boy 6 years of age who experienced sudden blindness 10 days following acute favism. Partial loss of sight rapidly became total. At this time the child appeared essentially normal by clinical examination and by laboratory

investigation. On ophthalmologic examination the pupils were moderately enlarged and responded only very slightly to light. The discs were prominent with blurred margins; the retinal vessels, particularly the arteries, were constricted. A few scattered hemorrhages were present in the proximity of the discs. Visual acuity consisted of hand movements only. Examination performed 2 weeks later showed pale discs with persisting blurred margins and narrowing of the arteries. However, the hemorrhages surrounding the discs were being absorbed rapidly. Visual acuity at this time consisted in finger counting. Within the next few weeks the disc margins became better defined, and the hemorrhages were absorbed completely. Visual acuity improved gradually. Two months following the onset of blindness the discs appeared pale but with margins well defined. The retinal vessels were still narrow; visual acuity in the right eye was 1/10 and in the left was 1/20. While the visual field examination was limited by the patient's age, central scotomas were observed with evidence of peripheral loss, particularly in the downward direction.

Although the ophthalmic complications in both these patients were associated with acute favism, the authors feel that the pathogenesis and the mechanism responsible for the ocular complications were not exactly the same in the 2 cases. In their opinion the manifestations in the first case resembled those reported in certain transfusion reactions. For example, disturbances of blood coagulation resulting in hemorrhagic phenomena have been described in patients with paroxysmal nocturnal hemoglobinuria following plasma transfusions. In these cases the hemorrhagic diathesis has been explained on the basis of intravascular coagulation presumably initiated by the thromboplastinlike activity of the hemolyzed red blood cells. According to the authors, "Such a concept appears to apply to [the] first patient who developed an acute hemorrhagic state with prolonged bleeding time and thrombocytopenia following an extensive hemolysis due to favism."[5] The possibility of incompatible blood for transfusion was eliminated to the authors' satisfaction. They are aware that the retinal and preretinal extravasation which occurred might be attributed to a generalized hemorrhagic state. Similar retinal hemorrhages have been described in association with idiopathic thrombocytopenic purpura. If the hemorrhages are restricted to the retina the prognosis is considered good, since they may be absorbed without causing permanent damage. On the other hand, when the hemorrhages into the hyaloid body are extensive and diffuse, the prognosis in general is considered to be poor, since the ensuing organization leads ultimately to retinal detachment.

In the case of the second patient the authors feel that the ophthalmologic complications are of somewhat more obscure pathogenesis. To their knowledge such ocular findings, blurring of the discs, papilledema, etc., with attendant changes, have not been reported in association with favism or other acute hemolytic syndromes, but resemble the clinical manifestations sometimes observed after acute hemorrhage. In summary, the authors emphasize that in favism and perhaps in drug-induced hemolytic anemias as well, ocular complications should be considered a possibility, and that such patients should be checked carefully for signs of ocular involvement, however minor the clinical episode of sensitivity may appear to be.

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Books

Leukaemia, Research and Clinical Practice.
F. G. J. Hayhoe, M.D., Boston, 1960, Little, Brown & Company, 335 pages. Price $16.00.

The rising incidence of leukemia together with the multitude of studies of its etiology require that the thoughtful physician look occasionally at the developments in the study of this disease as a possible herald of progress to be forthcoming in relation to other neoplasms. The advent of relatively specific, albeit not curative, forms of effective therapy require a greater familiarity not only with the initial manifestations of leukemia but also with the vagaries of therapy and the changes in prognosis which have been produced. Dr. Hayhoe has written an excellent book which admirably reviews all the current theories of etiology, the biochemistry of purines, and desoxyribose nucleic acid, and proceeds to a comprehensive summary of therapy and to a discussion of the specific types of leukemia. The portion of the book which discusses the specific types of leukemia includes descriptions not only of the manifestations and cellular morphology, but also, through illustrative case reports and charts, outlines the therapy which is recommended and the responses which may be anticipated from such therapy. This section is most comprehensively written and should be of value to many who see this illness only rarely. There are enough specific references to children to make clear the difference between leukemia in the adult and the child; even the work of Bozeman and associates regarding the emotional responses of the parents to the onslaught of leukemia in a child is covered.

Some sections of this book, particularly those concerned with etiology, may be read with profit by all physicians and the entire book should be valuable to anyone concerned with the treatment of leukemia. There are illustrations of good quality in both color and black and white, as might be anticipated, and the bibliography is quite comprehensive for those who wish to refer to original observations.

A. E. MC ELFRESH, M.D.

Fundamentals of Child Psychiatry.
Stuart M. Finch, M.D., New York, 1960, W. W. Norton and Company, 334 pages. Price $5.95.

The Department of Psychiatry of Temple University School of Medicine has produced some of the most useful books in child psychiatry. *Emotional Problems of Living* by English and Pearson, published in 1945, was the first of this series. Dr. Finch, formerly with the Temple group and now Associate Professor of Psychiatry and Director of the Children's Psychiatric Hospital, University of Michigan Medical School, has added a valuable companion volume to this series. His book presents in a very readable style the substance of modern clinical practice of child psychiatry. Case histories are liberally used to illustrate points. Throughout the book the reader is looking over the shoulder of the child psychiatrist as he conducts his diagnostic study, outlines a treatment plan, and carries it out. The use of the clinical psychiatric team, as well as individuals in the child's daily life, in treatment programs is clearly brought out.

Dr. Finch also makes it clear that the child psychiatrist is concerned with a wide variety of children, including those with psychosomatic disorders, mental retardation, cerebral palsy, and other handicapping conditions. He dispels the notion that child psychiatry is simply concerned with children with neurotic and behavior disorders. He includes a very useful and succinct chapter on psychotic reactions of childhood.

This volume is not addressed to the child psychiatry resident or the practicing child psychiatrist. It is not an encyclopedia of child psychiatry. It is particularly addressed to the medical student and the pediatrician who want a simple, basic, yet comprehensive book on child psychiatry, as well as to young psychologists, social workers, and educational specialists.

The reviewer hopes that in subsequent editions material will be included which outlines the place of child psychiatry within the framework of community health services, the relationship of such clinics to the private psychiatrist, the family

physician, the public school, the well child conference, and the various public and private social agencies. The practicing child psychiatrist today plays an important role in community programs of mental health education and consultation. In many instances he has taken leadership in this public health–mental health work. A chapter on this aspect of his professional role will round out the picture.

WARREN T. VAUGHAN, JR., M.D.

The Child in Hospital.
Hedley G. Dimock, Philadelphia, 1960, F. A. Davis Company, 236 pages. Price $4.50.

This book presents a comprehensive discussion of the nonmedical care of children in hospitals; it also contains an excellent bibliography on the psychosocial problems and management of the sick, hospitalized child.

Although there has been a need for this kind of material, from the point of view of the pediatrician, there are various shortcomings in this presentation because the doctor's role in meeting the emotional needs of hospitalized children is barely touched upon and the focus is entirely on the combined efforts of the paramedical hospital staff. This is unfortunate because many of the statements concerning the needs of the child in the hospital would be useful to the physician and medical student as well as to other personnel. It is my impression, however, that most physicians would be impatient with a presentation of this length which appears to relate to their functions only indirectly.

For nurses, social workers, occupational therapists, recreational workers, educators, and all others concerned with the day-to-day management of hospitalized children, I would highly recommend this work. There are good sections on the role of the parents in the child's hospital experience with a wholesome viewpoint on the positive contributions that the parents can make to the child's hospitalization and a flexible outlook on such problems as visiting hours, preparation for hospitalization, home care, etc. There is a good discussion on the way that children can be grouped on hospital wards and in recreational activity so as to make the hospital experience constructive for the child. There is also a pertinent discussion of interstaff relationships in the hospital as they affect the hospitalized child as well as the staff members themselves. The author clearly has a special interest in group techniques, group interaction, and the therapeutic use of group work and this pervades her discussions of many facets of hospital experience.

The weakest section of the book is the introduction in which Miss Dimock attempts to summarize her general philosophy and give a brief outline of child development to serve as the basis for subsequent discussions. In this section, she has attempted to cover a great deal of territory and, consequently, deals rather cavalierly with such complicated concepts as the child's need for a feeling of trust, rejection of children by their parents, etc.

In summary then, *The Child in Hospital* represents a thorough and detailed discussion of all aspects of the hospital milieu, the child's reaction to the hospital experience, the special needs of the hospitalized child, and how these can be met by the various members of the interdisciplinary staff active on a children's ward. All professional workers as well as volunteers concerned with the care of the hospitalized child could profit from reading this work. Many physicians actively involved in the administration, organization, or conduct of children's hospitals would also profit from certain portions of the book, but would probably find it a little too long winded and would miss more direct relevance to their own functions in the care of the child. For example, the simplified discussion of the functions of the psychologist or of the nature of play therapy for children would be of no interest to physicians nor would the physician be concerned with the detailed discussion of the activities of the group leader in pediatric recreation. In contrast, the section on parents' role in the child's hospital experience would be very helpful for many pediatricians.

To end on a lighter note, there is in this book a lovely quotation from a child subjected to the routine, old-fashioned kind of occupational therapy, "Here I sit at a great big loom, making God knows what for God knows whom."

BARBARA KORSCH, M.D.

News and notes

The American Psychosomatic Society will hold its eighteenth annual meeting at Chalfonte-Haddon Hall, Atlantic City, April 28 to 30, 1961. Titles and abstracts of papers for consideration for the program must be submitted by December 1. Abstracts should be submitted with 9 copies and should not be more than 2 typewritten pages. Time allotted for presentation of each paper will be 20 minutes.

Abstracts should be addressed to Morton F. Reiser, M.D., Chairman, Program Committee, 265 Nassau Road, Roosevelt, New York, N. Y.

The Department of Pediatrics, Ohio State University College of Medicine and the Columbus Children's Hospital will sponsor a postgraduate course for pediatricians on **The Undergrown Child,** March 22 to 24, 1961. Designed to cover practical points about growth failure, its causes, implications, and treatment, the course will be held in conjunction with the Annual Alumni Day of the Children's Hospital. The local faculty will be augmented by visiting professors. Attendance will be limited to 75; registration fee is $45.00. For details write to William O. Robertson, M.D., Department of Pediatrics, The Children's Hospital, Columbus 5, Ohio.

Residencies and traineeships in pediatric hematology and oncology are available for July, 1961, at the Children's Hospital of Los Angeles, Department of Pediatrics, University of Southern California. Applicants for residency (fellowship) in pediatric hematology should have completed pediatric training acceptable for certification by the American Board of Pediatrics.

The traineeship program is designed to prepare participants for careers in academic medicine and research. Applicants should have completed 3 or more years of training beyond internship. Some previous experience in clinical hematology or a preclinical science related to hematology is desirable. Preference will be given for a training period of 2 years or more.

For further information write to Denman Hammond, M.D., Children's Hospital of Los Angeles, 4570 Sunset Boulevard, Los Angeles 27, Calif.

A postgraduate course in allergy is being offered by the Departments of Allergy and Applied Immunology of the Temple University Medical Center and the Graduate School of Medicine of the University of Pennsylvania at Temple Medical Center, February 27 to March 10. Emphasis will be on methods of diagnosis and management of the allergic patient.

Tuition is $175.00. For further information contact Dr. George Blumstein, Temple Medical Center, Philadelphia 40, Pa.

A postgraduate course in general pediatrics will be offered by the University of Arkansas, December 7-8 in cooperation with the Arkansas Medical Society, the Arkansas Academy of General Practice, and the Arkansas Academy of Pediatrics. It will be presented by the Department of Pediatrics under the direction of Dr. Theodore C. Panos, Professor and Chairman. Guest participants will include Dr. Amos U. Christie and Dr. Edward L. Pratt. All practitioners are welcome.

For information regarding registration write to the Office of Post-Graduate Medicine at the University of Arkansas Medical Center, Little Rock, Ark.

EDITOR'S COLUMN

The mystery of Indian childhood cirrhosis

SINCE Sen's[1] original and classical account in Bengal in 1887, the cirrhosis of the liver found not uncommonly in eastern India has continued to pose a series of intriguing and as yet unsolved problems.

Basically, as noted in the recent papers by two of India's most distinguished pediatricians, S. T. Achar[2] and K. C. Chaudhuri,[3] and their colleagues, the usual picture is of an insidious onset with initial, rather vague, mainly gastrointestinal and general features. Enlargement of the liver is the first really suggestive sign ("stage of hepatomegaly")[4] and the disease is established beyond doubt with the development of a collateral circulation, ascites, a hard, irregular liver, and splenomegaly, followed, ultimately, by some degree of jaundice and death in cholemia, from secondary infection or as a result of hemorrhage from esophageal varices ("stage of clinical cirrhosis").[4]

The first problem lies with early diagnosis, especially in view of the commonness of vague gastrointestinal features in young children in India, and also the probable multiplicity of causes of hepatomegaly in a tropical environment, including, for example, the result of repeated transhepatic migration of Ascaris larvae. This means in practice that it is extremely difficult—or, indeed, impossible—to make a firm early diagnosis on clinical grounds, except via the biased wisdom of hindsight. Undoubtedly many "cures" of alleged early Indian childhood cirrhosis must, in fact, be related to unproved and incorrect diagnosis.

Even the name of the condition is controversial, although it does seem reasonably apt and, at the same time noncommittal, to call it "Indian *childhood* cirrhosis." Patients are, in fact, almost always beyond the period of actual infancy, as witness the recent series from Calcutta.[3] Chaudhuri[3] is of the view that, as judged by amino acid metabolism, the condition may, in fact, be a syndrome (Sen's syndrome) made up of two or more entities.

The histology of Indian childhood cirrhosis (giving as it may clues as to possible etiology) has been, on the whole, rather inadequately studied, mainly because of the extreme difficulty of obtaining autopsies in India, so that liver biopsy material has mostly been employed. Again, results have not been in entire agreement. However, the majority of Indian investigators have found diffuse liver cell damage and replacement fibrosis[5] to be the dominant features histologically, and these were the findings in Achar's[2] cases from Madras. By contrast, Jelliffe, Bras, and Mukherjee[4] noted occlusion of hepatic vein radicals in some of their cases, resembling the picture seen in subacute and chronic venoocclusive disease of the liver in Jamaican children.[6] The clinical picture of Indian childhood cirrhosis resembles in many ways that of subacute or chronic venoocclusive disease, but, as Achar[2]

remarks, the sudden onset with hepatomegaly and ascites seen in the acute stage, observed in a minority of Jamaican cases, has never been seen in Indian childhood cirrhosis.

The etiology of the disease is unknown. Achar and his colleagues are of the opinion that the late effects of a form of viral hepatitis are most likely and have shown that Indian childhood cirrhosis, and both acute and persistent forms of hepatitis are all common in the 1 to 5 year age group in Madras. In the past so many hypotheses have been brought forward (including malnutrition, unbalanced nutrition, excess of spices, infection with *Escherichia coli*, etc.) that the syndrome has been called the "disease of theories." None, so far, is proved, although it is generally agreed that malnutrition does *not* play a dominant role. The possibility of dual insults to the liver requires consideration; the same type of double etiology has been suggested in the fibrosis of the liver found in Gambian children in West Africa, where Walters and Waterlow[7] were of the opinion that combined malnutrition and chronic *Plasmodium falciparum* malaria were jointly responsible.

Plainly more investigation is needed, although it is difficult to suggest the most fruitful approaches. Further longitudinal histologic studies, such as those reported by Achar,[2] would be important, especially if completed, in fatal cases, with the infinitely more inspection possible at autopsy; while, as Achar suggests, search for an etiological virus must be carried out with modern techniques.

D. B. JELLIFFE, M.D.

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Patterns of serum transaminase activity—diagnostic aid in neonatal jaundice

THE recent expansion in knowledge of bilirubin metabolism has resulted in a clearer understanding of the physiology of neonatal jaundice.[1-3] Nevertheless, this syndrome continues to present frustrating problems in etiological diagnosis, despite the progress which has been made in the elucidation of fundamental biochemical processes. Jaundice in the neonatal period may be caused by a multiplicity of conditions, from benign to serious; some are duplicated in older children and adults, and others are peculiar to this early period of life. The following are the more frequent causes:

1. Physiologic jaundice of the newborn.

2. Hemolytic states (blood group incompatibility, hereditary spherocytosis, instability of reduced glutathione or reduced glucose-6-phosphate dehydrogenase activity of erythrocytes, noxious agents, etc.).

3. Infections, intrahepatic or extrahepatic (sepsis, syphilis, toxoplasmosis, cyto-

megalic inclusion disease, leptospirosis, herpes simplex).

4. Metabolic disturbances (galactosemia, cretinism, familial nonhemolytic jaundice).

5. So-called "inspissated-bile syndrome" (including type occurring in course of hemolytic conditions and type resulting from undetermined factors).

6. Congenital malformations of bile ducts (extrahepatic or intrahepatic).

7. Acute neonatal viral hepatitis (serologic or infectious types).

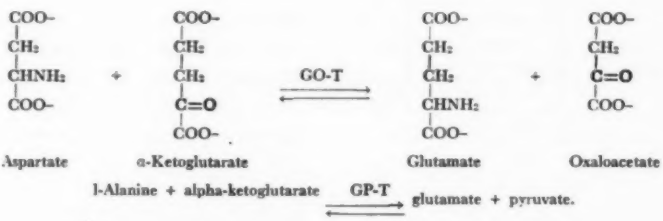
In this early period of life, in contrast to the situation in adults, the usual diagnostic modalities are often of limited value in delineating the cause of icterus. The history is frequently inadequate, erroneous, or misleading, and the information obtained from physical examination and the usual laboratory procedures may be wholly inconclusive. Against this background the need has long existed for a diagnostic technique which would be of material aid in the etiological diagnosis of neonatal jaundice.

Such a diagnostic tool has been reported by the writer and his colleagues.[4-7] The results of these preliminary studies, which have been in progress since 1956, appear to indicate that serial measurements of transaminase* activity in serum are of significant value in establishing the etiological category of jaundice in the neonatal period and very early infancy. Two groups of infants were studied: one of normal newborn infants to establish normal values for this age group and another of infants with jaundice due to various pathologic conditions. The infants in the group with jaundice of pathologic origin varied in age from birth to 3 months at the time of initial observation, with the single exception of a 5-month-old premature infant (7 months' gestation). From all infants in this group frequent serial measurements of serum enzyme activity were obtained for glutamic oxaloacetic transaminase (GO-T) and glutamic pyruvic transaminase (GP-T). From these studies it was found that characteristic patterns of enzyme activity appeared to evolve for the varied causes of neonatal jaundice, thereby facilitating diagnosis. The findings may be summarized as follows:

1. Normal newborn infants. In the early neonatal period levels of activity up to 120 units for GO-T and up to 90 units for GP-T were found to be normal (range in normal adults is 5 to 40 units). At 2 to 3 months of age the normal range of enzyme activity is similar to that in adults.

2. Neonatal jaundice associated with neonatal hyperbilirubinemia, prolonged neonatal hyperbilirubinemia, absorption of components from encapsulated hematoma, cretinism,[8] extrahepatic infection, incom-

*Transaminases are enzymes which catalyze reactions involving the transfer of an amino group (NH_2) from an amino acid to a keto acid with the formation of a new amino acid and a new keto acid. A number of transaminases have been identified. Two of these, glutamic oxaloacetic transaminase (GO-T) and glutamic pyruvic transaminase (GP-T), have been found useful in the diagnosis of hepatic disease and are involved in the following reactions:



The enzymes are widely distributed in human and animal tissues, and are also present in normal serum and plasma. The liver is particularly rich in transaminase activity. An increase in enzyme activity in serum results from hepatocellular injury and/or necrosis due partly to the liberation of the enzymes from the damaged cells. Enzyme activity is measured spectrophotometrically and the results are expressed as units per milliliter of serum per minute.

plete biliary obstruction in the "inspissated bile syndrome," and kernicterus. Normal neonatal levels of enzyme activity were found in all of these conditions.

3. Neonatal jaundice due to hemolytic states. Regardless of cause these conditions were usually characterized by normal neonatal levels of enzyme activity. However, severe fulminant hemolysis was associated with a transient increase limited to GO-T to about 300 units.

4. Neonatal jaundice due to complete biliary obstruction (exclusive of hepatitis). Serum transaminase activity increased relatively slowly but progressively to a peak below 800 units. Thereafter, it leveled off to a lower, although increased, range. It further appears that the "medical" type of neonatal jaundice (so-called inspissated bile syndrome) may be differentiated from the "surgical" type (congenital malformation of bile ducts). In the "medical" type the increase in serum transaminase activity began early in the neonatal period (during the first week of life). In contrast, in the "surgical" type the increase in enzyme activity began later in the neonatal period (at about 1 to 1½ months of age).

5. Neonatal jaundice associated with hepatic cirrhosis (secondary to malformation of the biliary tract). Serum transaminase activity was generally increased to variable levels below 800 units, with GO-T usually being higher than GP-T. At times enzyme activity may not be increased, presumably as a reflection of inactivity in the cirrhotic process.

6. Neonatal jaundice due to cytomegalic inclusion disease with hepatic involvement. GO-T activity was increased from birth at a sustained plateau range of 300 to 400 units in the single infant studied (GP-T was not studied).

7. Jaundice associated with acute neonatal viral hepatitis (serologic type). Enzyme activity rose sharply and rapidly during the stage of increasing hyperbilirubinemia. The peak level for GO-T was well above 800 units (1,140) in this infant with the mildest detectable clinical manifestations of the disease. The increase in GP-T was less striking.*

The necessity for early and accurate diagnosis in neonatal jaundice is not merely academic but stems from urgent prognostic and therapeutic considerations. Thus, in conditions of the biliary tract correctable by surgery, delay in definitive therapy may well compromise the ultimate favorable prognosis by permitting the progression of the cirrhotic process. Formerly it was believed that cirrhosis developed in congenital extrahepatic malformations only after prolonged biliary obstruction. On the contrary, in recent years it has been demonstrated that cirrhosis actually begins early in the course of this biliary malformation, i.e., at about 4 to 6 weeks of age, and it is well established at the age of 2 to 3 months.[9] Thus, in infants with jaundice due to reparable "surgical" lesions, optimal ultimate results may be expected only by early diagnosis and therapy.[10, 11, 12] It may be noted that the initial increase in serum transaminase activity which has been demonstrated to occur at about 1 to 1½ months of age in congenital biliary malformation is probably a reflection of the onset of hepatic damage and cirrhosis.

Early definitive diagnosis is equally important in "medical" types of neonatal jaundice as it is in the "surgical" types. By this means an effective deterrant may be provided against resorting to surgical exploration for a solution of the diagnostic problem. For, in infants with jaundice due to "medical" conditions, surgical interference may adversely affect the clinical course and is therefore contraindicated.

It cannot be emphasized too strongly that the value of this laboratory procedure rests upon serial measurements of serum transaminase activity, rather than on a single isolated determination. Although a single measurement may yield pertinent information a

*Undoubtedly acute neonatal viral hepatitis may be reflected in a peak level of transaminase activity below 800 units. In this instance, the disease would probably present clinically in the anicteric form, and would therefore not present a problem in differential diagnosis of neonatal jaundice.

a given stage of an icteric disease, it may also even be misleading if accepted at face value and not related to the clinical course.

The stress which is laid upon serial rather than single measurements of serum transaminase activity does not detract from its importance as a valuable aid in the early diagnosis of neonatal icterus. For practical purposes, once the enzyme patterns for the varied disturbances associated with icterus in early infancy have been delineated, it is not necessary or desirable to await the complete elaboration of the enzyme pattern before arriving at a definitive diagnostic conclusion. Adequate clues for early diagnosis may often be supplied from the initial enzyme alterations as related to the clinical course without the necessity of awaiting prolonged observations. The following three consecutively studied infants who recently came under observation and were found to have congenital malformations of the biliary tracts furnish dramatic illustrations of early diagnoses which were accomplished only by virtue of the enzyme patterns:

Case 1. A 1-month-old premature infant with biliary obstruction. A definitive diagnosis of congenital malformation of the bile ducts was made after 2 weeks (at 1½ months of age) when serum transaminase activity started to increase above the normal range. At operation atresia of the entire extrahepatic biliary tract was found.

Case 2. A 1½-month-old infant with jaundice, purulent meningitis, and pyuria. A diagnosis of congenital malformation of the biliary tract as an associated lesion was made 1 week after admission to the hospital on the basis of the evolution of the pattern of serum transaminase activity. The findings on postmortem examination were intrahepatic biliary atresia, purulent meningitis, and renal abscesses.

Case 3. An 8 pound jaundiced infant with no history available. A diagnosis of congenital malformation of the biliary tract was made on the fourth hospital day because serum transaminase activity increased from initially normal levels. A choledochal cyst was found at operation.

Needless to say, in addition to patterns of serum transaminase activity, accurate historical data and discriminate interpretation of the physical findings, clinical course, and other laboratory data are of importance in facilitating a diagnosis in young infants with jaundice. As may be anticipated with any diagnostic modality there are certain limitations in the utilization of serial measurements of serum transaminase activity. Thus, enzyme studies may yield only limited information, if observations are initiated too late in the course of the disease for characteristic patterns to evolve.

SIMON KOVE, M.D.

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Pan-American Pediatric Congress

THE Pediatric Congress held during August in Caracas was a combined meeting of three organizations: The Pan-American Congress of Pediatrics (VI), the South American Congress of Pediatrics (VI), and the Venezuelan Congress of Pediatrics (I).

Although most of those attending were from Venezuela and secondarily from other South American countries, there was fair representation from Central American countries, Mexico, the West Indies, and the United States. There is real value in such a meeting, not only from the scientific aspect, but also for the opportunity provided the teachers of pediatrics to become better acquainted and to share experiences and thinking in relation to teaching methods.

One session was devoted to a discussion of curricular plans and teaching methods. From it came a suggestion that a society of pediatric teachers within the Western Hemisphere be organized. Such a society could have potential not only as a forum to evaluate teaching practices, but also to encourage and influence greater financial support for the pediatric departments in all of the schools. It was encouraging to note that there was consensus in favor of full-time teachers as the nucleus of the pediatric departmental staff.

The program of the meeting was excellent with good participation from the floor. The physical arrangements were well above par and, on both the serious and lighter sides, the meeting set a high goal for subsequent Pan-American meetings to equal.

Dr. Eduardo Urdaneta as Secretary General and his committees and co-workers deserve much credit for the arrangements of the program and for its smooth direction. It was a privilege to participate and we will look forward with anticipation to the next and subsequent Pan-American congresses.

W. E. N.

Brazilian Society of Pediatrics, fiftieth anniversary

OVER 800 pediatricians and their wives from the vast reaches of Brazil celebrated the fiftieth anniversary of the founding of the Brazilian Society of Pediatrics in July in Rio de Janeiro, with guests from Argentina, Uruguay, France, Portugal, Italy, and the United States. The meeting was held under the presidency of Dr. Alvaro Aguiar.

A wide variety of subjects was discussed with special emphasis on the social aspects of pediatrics and preventive care programs. The excellent scientific program was matched by the ample social activities with Brazilian pediatricians opening their homes to the visitors.

The year 1960 marks the organization of a separate district in the Academy in Brazil, District XI, under the chairmanship of Dr. Rinaldo de Lamare.

H. B.